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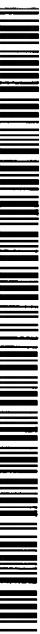
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A1

(54) Title: 3,6-DISUBSTITUTED AZABICYCLO [3.1.0] HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to derivatives of 3,6-disubstituted azabicyclo [3.1.0] hexanes of structure (I). The compounds of this invention can function as muscarinic receptor antagonists, and can be used for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to pharmaceutical compositions containing the compounds of the present invention and the methods for treating the diseases mediated through muscarinic receptors.



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3,6-DISUBSTITUTED AZABICYCLO [3.1.0] HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to the derivatives of 3,6-disubstituted azabicyclo[3.1.0]hexanes. The compounds of this invention can function as muscarinic receptor antagonists, and can be used for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors.

The invention also relates to pharmaceutical compositions containing the compounds of the present invention and the methods of treating the diseases mediated through muscarinic receptors.

BACKGROUND OF THE INVENTION

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are composed of a family of 5 receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented. For example, the M_1 subtype is located primarily in neuronal tissues such as cerebral cortex and autonomic ganglia, the M_2 subtype is present mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (*Nature*, 1986; 323: 411; *Science*, 1987; 237: 527).

A review in *Current Opinions in Chemical Biology*, 1999; 3: 426, as well as in *Trends in Pharmacological Sciences*, 2001; 22: 409 by Eglen et. al., describe the biological potentials of modulating muscarinic receptor subtypes by ligands in different disease conditions like Alzheimer's disease, pain, urinary disease condition, chronic obstructive pulmonary disease etc.

A review in *J. Med. Chem.*, 2000; 43: 4333 by Christian C. Felder et. al. describes therapeutic opportunities for muscarinic receptors in the central nervous

system and elaborates on muscarinic receptor structure and function, pharmacology and their therapeutic uses.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in Molecules, 2001,

5 6: 142.

N.J.M. Birdsall et. al. in Trends in Pharmacological Sciences, 2001; 22: 215 have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptors of knock out mice.

Muscarinic agonists such as muscarine and pilocarpine and antagonists such
10 as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as
15 tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly derivatives of atropine such as ipratropium bromide are better tolerated than parenterally administered options but most of them are not ideal anti-cholinergic bronchodilators due to lack of selectivity for muscarinic receptor sub-types. The existing compounds offer limited therapeutic benefit due to
20 their lack of selectivity resulting in dose limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as tachycardia mediated by the M₂ receptor.

Annual Review of Pharmacological Toxicol., 2001; 41: 691, describes the pharmacology of the lower urinary tract infections. Although anti muscarinic agents
25 such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (W.D.Steers et. al. in Curr. Opin. Invest. Drugs, 2:
30 268, C.R. Chapple et. al. in Urology, 55: 33), Steers WD, Barrot DM, Wein AJ, 1996, Voiding dysfunction: diagnosis classification and management. In "Adult and

Pediatric Urology," ed. JY Gillenwatter, JT Grayhack, SS Howards, JW Duckett, pp 1220-1325, St. Louis, MO; Mosby. 3rd edition.)

Despite these advances, there remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus
5 avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601.
10 U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstituted piperidine derivatives; WO 93/16018 and WO96/33973 are other references.

A report in J. Med. Chem., 2002; 44:984, describes cyclohexylmethyl
15 piperidinyl triphenylpropioamide derivatives as selective M₃ antagonist discriminating against the other receptor subtypes.

SUMMARY OF THE INVENTION

The present invention provides derivatives of 3,6-disubstituted azabicyclo[3.1.0]hexanes as muscarinic receptor antagonists and are useful for the
20 safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems, and process for the synthesis of the novel compounds.

The invention also provides pharmaceutical compositions containing the compounds, and which may also contain acceptable carriers, excipients or diluents
25 which are useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

The present invention also includes within its scope prodrugs of the compounds. In general, such prodrugs are functionalized derivatives of these compounds which readily get converted *in vivo* into the defined compounds.

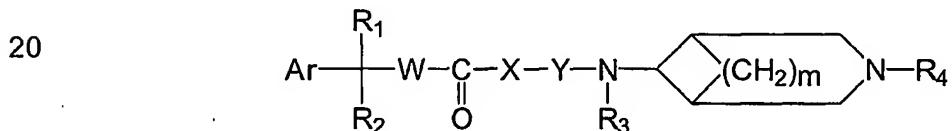
Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan of ordinary skill in the art.

The invention also includes the enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts, pharmaceutically acceptable 5 solvates, esters and metabolites of these compounds having the same type of activity.

The invention further includes pharmaceutical compositions comprising the compounds of the present invention, their prodrugs, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts, 10 pharmaceutically acceptable solvates or esters, in combination with a pharmaceutically acceptably carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows and in part will be apparent from the description or may be learnt by the practice of the invention. The objects and the advantages of the invention may be 15 realized and obtained by means of the mechanisms and combinations pointed out in the appended claims.

In accordance with one aspect of the present invention, there is provided a compound having the structure of Formula I:



Formula I

25 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein:

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings 30 may be unsubstituted or substituted by one to three substituents independently selected from straight or branched lower alkyl (C₁-C₄), trifluoromethyl,

methylenedioxy, cyano, hydroxy, halogen (e.g. F, Cl, Br, I), nitro, lower alkoxy (C₁-C₄), aryloxy, amino or lower alkylamino;

R₁ represents C₃-C₉ cycloalkyl ring, a C₃-C₉ cyclo alkenyl ring, an aryl or a heteroaryl ring having 1 to 2 hetero atoms selected from the group consisting of oxygen,

5 sulphur and nitrogen atoms, the aryl or a heteroaryl ring may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), unsubstituted amino or lower alkyl (C₁-C₄) amino;

R₂ represents a hydrogen, hydroxy, amino, alkoxy, alkenyloxy, alkynyoxy,

10 carbamoyl or halogen (e.g. F, Cl, Br, I);

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR, or no atom, where R is H or lower alkyl (C₁-C₄);

Y represents (CHR₅)_q CO wherein R₅ represents hydrogen, or methyl; or Y

15 represents (CH₂)_q wherein q represents 0 to 4;

m represents 0 to 2;

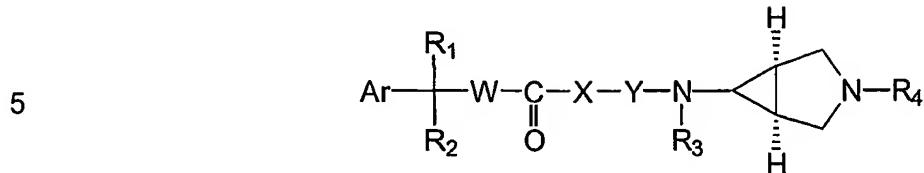
R₃ represents hydrogen, lower alkyl or CO₂C (CH₃)₃;

R₄ represents hydrogen, C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon

groups in which any 1 to 6 hydrogen atoms may be substituted with the group

20 independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, carboxylic acid, 25 nitro, lower alkoxy carbonyl, halogen, lower alkoxy, amino, lower alkylamino, loweralkyl carbonyl amino, loweralkyl thiocarbonyl amino or loweralkyl carbonyl amino sulphonyl and pharmaceutically acceptable salts thereof.

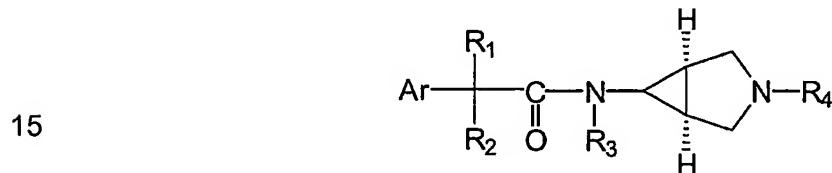
More particular compounds of the present invention are represented by Formula II,



Formula II

10 wherein Ar, R₁, R₂, R₃, R₄, W, X and Y are as defined for Formula I.

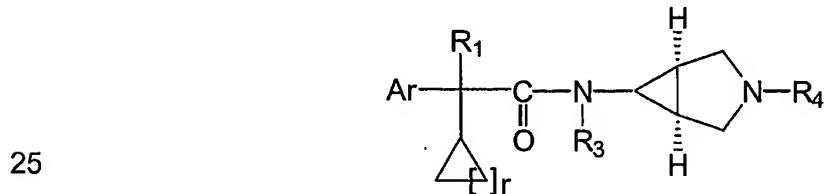
Further particular compounds are represented by Formula III



Formula III

wherein Ar, R₁, R₂, R₃ and R₄ are as defined for Formula I.

20 Still more particular compounds are represented by Formula IV

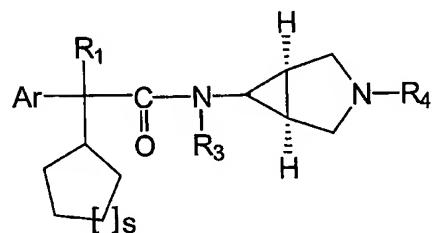


Formula IV

wherein Ar, R₁, R₃ and R₄ are as defined for Formula I and r is 1 to 4.

Still more particular compounds are represented by Formula V

5

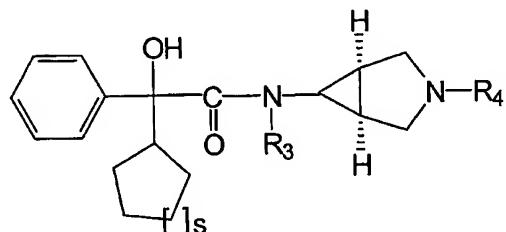


Formula V

10 wherein Ar, R₁, R₃ and R₄ are as defined for Formula I and s is 1 to 3.

Another particular compound is represented by Formula VI,

15



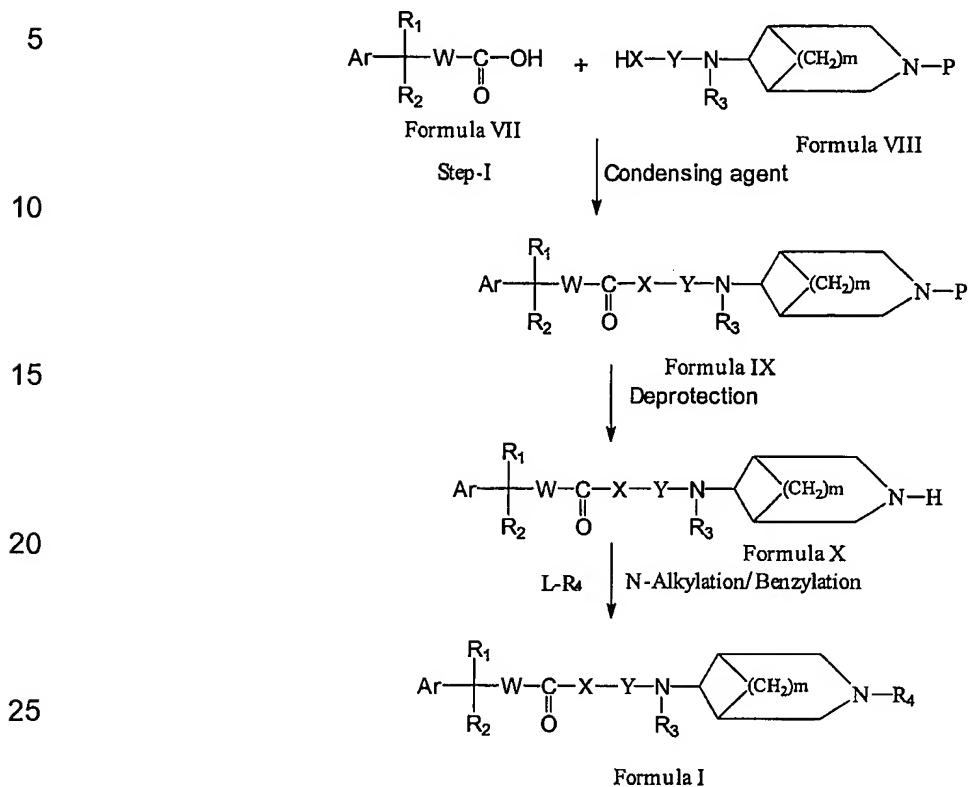
20

Formula VI

wherein R₃, R₄ and s are as defined for Formula V.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared by the reaction sequence as shown in Scheme I



Scheme I

30 The preparation comprises condensing a compound of Formula VII with the compound of Formula VIII wherein:

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from straight or branched lower alkyl (C_1-C_4), trifluoromethyl, methylenedioxy, cyano, hydroxy, halogen (e.g. F, Cl, Br, I), nitro, lower alkoxy (C_1-C_4), aryloxy, amino or lower alkylamino:

R_1 represents C_3 - C_9 cycloalkyl ring, a C_3 - C_9 cyclo alkenyl ring, an aryl or a heteroaryl ring having 1 to 2 hetero atoms selected from the group consisting of oxygen,

sulphur and nitrogen atoms, the aryl or a heteroaryl ring may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), unsubstituted amino or lower alkyl (C₁-C₄) amino;

5 R₂ represents a hydrogen, hydroxy, amino, alkoxy, alkenyloxy, alkynyoxy, carbamoyl or halogen (e.g. F, Cl, Br, I);

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR, or no atom, where R is H or lower alkyl (C₁-C₄);

10 Y represents (CHR₅)_q CO wherein R₅ represents hydrogen, or methyl; or Y represents (CH₂)_q wherein q represents 0 to 4;

m represents 0 to 2;

R₃ represents hydrogen, lower alkyl or CO₂C(CH₃)₃;

P is any group which can be used to protect an amino group, for example benzyl and t-butyloxycarbonyl, in the presence of a condensing agent, for example 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide hydrochloride (EDC) or 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), to give a protected compound of Formula IX wherein R₁, R₂, R₃, W, X, Y, P and m are the same as defined earlier. The compound of Formula IX on deprotection through reaction with a deprotecting agent, for example palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid, in an organic solvent gives an unprotected compound of Formula X wherein R₁, R₂, R₃, W, X, Y and m are the same as defined earlier. Compounds according to Formula X (with R₄ as hydrogen) are useful as muscarinic receptor antagonists, and are useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems. These compounds can be formulated as pharmaceutical compositions for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems. Compounds of Formula X can be optionally N-alkylated or benzylated with a suitable alkylating or benzylating

agent L-R₄ to give a compound of Formula I, wherein L is any leaving group, for example halogen, O-mestyl or O-tosyl group, and

R₄ represents hydrogen, C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group
 5 independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, carboxylic acid,
 10 nitro, lower alkoxy carbonyl, halogen, lower alkoxy, amino, lower alkylamino, loweralkyl carbonyl amino, loweralkyl thiocarbonyl amino or loweralkyl carbonyl amino sulphonyl and pharmaceutically acceptable salts thereof.

In the above scheme, where specific bases, condensing agents, protecting groups, deprotecting agents, N-alkylating/benzylating agents, solvents, catalysts etc.
 15 are mentioned, it is to be understood that other bases, condensing agents, protecting groups, deprotecting agents, N-alkylating/benzylating agents, solvents, catalysts etc. known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

An illustrative list of particular compounds according to the invention and
 20 capable of being produced by Scheme I include:

Compound No.	Chemical Name	
1.	(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-diphenyl acetamide,	
25	2.	(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(4-fluoro phenyl) acetamide,
3.	(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenyloxy)-2,2-diphenyl acetamide,	
4.	(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenyloxy)-2,2-di(4-fluorophenyl) acetamide,	

5. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-propyloxy-2,2-diphenyl acetamide,
6. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-propyloxy-2,2-di(4-fluoro phenyl) acetamide,
- 5 7. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propynyoxy)-2,2-diphenyl acetamide,
8. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(2-furyl) acetamide,
9. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(2-thienyl) acetamide,
- 10 10. (1 α ,5 α ,6 α)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonylbutyl-1-(2-hydroxy-2,2-diphenyl)acetate,
11. (1 α ,5 α ,6 α)-3-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonylpropyl-1-(2-hydroxy-2,2-diphenyl)acetate,
- 15 12. (1 α ,5 α ,6 α)-3-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonyl propyl-1-(2-propynyoxy-2,2-diphenyl) acetate,
13. (1 α ,5 α ,6 α)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyl oxy carbonylbutyl-1-(2-propyloxy-2,2-diphenyl)acetate,
- 20 14. (1 α ,5 α ,6 α)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyl oxy carbonyl butyl-1-(2-(2-propenyoxy)-2,2-diphenyl) acetate,
15. (1 α ,5 α ,6 α)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyl oxy carbonylbutyl-1-(2-hydroxy-2,2-di(4-fluorophenyl))acetate,
16. (1 α ,5 α ,6 α)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyl oxy carbonyl butyl-1-(2-propyloxy-2,2-di(4-fluorophenyl)) acetate,
- 25 17. (1 α ,5 α ,6 α)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido-2-(2-propyloxy)-2,2-diphenyl acetate,
18. (1 α ,5 α ,6 α)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido-2- (2-propynyoxy)-2,2-diphenyl acetate,
- 30 19. (1 α ,5 α ,6 α)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-propionamido-2- (2-propenyoxy)-2,2-diphenyl acetate,

20. ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-propionamido-
2- 2-propyloxy)-2,2-diphenyl acetate,

21. ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido -2-
hydroxy-2,2-di(4-fluorophenyl) acetate,

5 22. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-
hydroxy- 2-phenyl acetamide,

23. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,5-difluorobenzyl))- 2- cyclo
hexyl-2-hydroxy-2-phenyl acetamide,

10 24. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-bromobenzyl))-2-cyclo
hexyl-2-hydroxy-2-phenyl acetamide,

25. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2,6-difluorobenzyl)) -2- cyclo
hexyl- 2-hydroxy-2-phenyl acetamide,

26. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylbenzyl))-2-
cyclohexyl-2-hydroxy-2-phenyl acetamide,

15 27. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylethyl))-2-cyclohexyl-
2-hydroxy-2-phenyl acetamide,

28. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(2,3-dihydrobenzo furan-5-
yl) ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

20 29. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(3,4-methylene
dioxyphenyl) ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

30. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-(2,3-dihydrobenzo furan-5-
yl) acetyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

31. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(benzofuran-5-yl)ethyl))-2-
cyclo hexyl-2-hydroxy-2-phenyl acetamide,

25 32. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-methyl)-2-cyclohexyl-2-
hydroxy- 2-phenyl acetamide,

33. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-ethyl)-2-cyclohexyl-2-hydroxy-
2-phenyl acetamide,

30 34. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-propyl))-2-cyclohexyl-2-
hydroxy-2-phenyl acetamide,

35. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propargyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

36. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

5 37. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

38. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-cyclopropyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

10 39. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-butyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

40. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3-methyl-2-but enyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

41. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

15 42. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,4-methylenedioxybenzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

43. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(6,6-dimethyl-2,4-heptadiynyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

20 44. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzoyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

45. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-formyl-fur-5-yl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

46. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(aniline)thiourea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

25 47. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(methyl, 4-amino-1-phenylacetate)urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

48. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-amino-1-phenyl acetic acid)urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

30 49. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methylphenyl-1-sulphonamide)urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

50. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl) acetamide,

51. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide,

5 52. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-phenoxyphenyl) acetamide,

53. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide,

10 54. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(3,4-methylenedioxophenyl) acetamide,

55. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-tertbutylphenyl) acetamide,

56. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl) acetamide,

15 57. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide,

58. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide,

20 59. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide,

60. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-ethyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide,

61. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-(2-propenyl)-2-phenyl acetamide,

25 62. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-methoxy-2-phenyl acetamide,

63. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2,4-difluorobenzyl))-2-cyclohexyl-2-methoxy-2-phenyl acetamide,

30 64. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

65. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

66. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(3,4-methylenedioxy phenyl) ethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

5 67. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

68. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(2,3-dihydrobenzofuran-5-yl)ethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

10 69. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-methyl-pyrid-6-yl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

70. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-(2,3-dihydrobenzofuran-5-yl) acetyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

71. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(benzofuran-5-yl)ethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

15 72. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cycloheptyl-2-hydroxy-2-phenyl acetamide,

73. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cycloheptyl-2-hydroxy-2-phenyl acetamide,

20 74. 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

75. 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) acetamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

76. 3-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

25 77. (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-3-cyclohexyl-3-hydroxy-3-phenyl propionamide,

78. 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) acetamido)-3-cyclohexyl-3-hydroxy-3-phenyl propionamide,

30 79. 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-3-hydroxy-3-phenyl propionamide,

80. ($1\alpha,5\alpha,6\alpha$)-2-[6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl-)-N-propionamido-2-cyclohexyl-2-hydroxy-2-phenyl acetate,

81. ($(2R)$)($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

5 82. ($(2R)$)($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,4-methylene dioxyphenyl)ethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide, or a pharmaceutically acceptable salts thereof.

The following salts of particular compounds were prepared:

10 83. ($(2R)$)-($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide succinate salt,

84. ($(2R)$)-($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide L-(+)-tartrate salt,

85. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide,

15 86. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide,

87. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl)acetamide,

20 88. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl)acetamide,

89. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide,

90. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cycloheptyl-2-hydroxy-2-phenyl acetamide,

25 91. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclobutyl-2-hydroxy-2-phenyl acetamide,

92. ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclopropyl-2-hydroxy-2-phenyl acetamide,

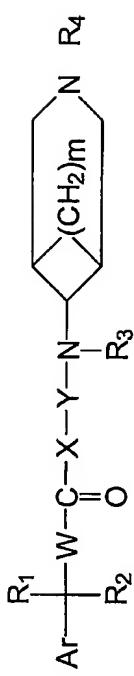
30 93. ($1\alpha,5\alpha,6\alpha$)-1-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-acetamido-2-hydroxy-2-cyclohexyl-2-phenylacetate,

94. ($1\alpha,5\alpha,6\alpha$)-1-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-propionamido-2-hydroxy-2-cyclohexyl-2-phenylacetate,

95. $(1\alpha,5\alpha,6\alpha)$ -4-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-(tert-butyloxy carbonyl)butyl-1-[2-hydroxy-2,2-bis(4-fluorophenyl)]acetate,
96. $(1\alpha,5\alpha,6\alpha)$ -4-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-(tert-butyloxy carbonyl)butyl-1-[2-propyloxy-2,2-bis(4-fluorophenyl)]acetate,
- 5 97. $(1\alpha,5\alpha,6\alpha)$ -6N-(3-azabicyclo[3.1.0]hexyl)-2,2-diphenyl acetamide,
98. $(1\alpha,5\alpha,6\alpha)$ -6N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-methoxy-2-phenylacetamide

10

The illustrated list of some particular compounds represented by Formula I is also given in Table I.

TABLE I
FORMULA I ($m=0$)

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
1.			OH	-	-	-	H	
2.			OH	-	-	-	H	
3.			O	-	-	-	H	
4.			O	-	-	-	H	
5.			O	-	-	-	H	

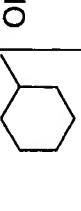
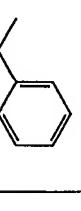
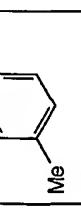
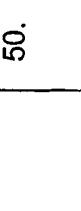
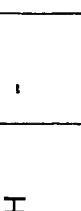
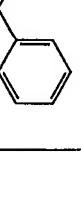
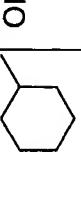
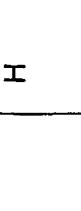
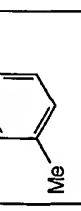
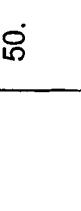
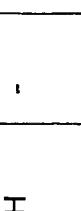
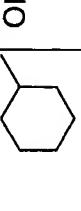
Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
6.			-	-	-	H		
7.			-	-	-	H		
8.			-	-	-	H		
9.				-	-	-		
10.				-	0	(CH ₂) ₄		
11.				-	0	(CH ₂) ₃		
12.				-	0	(CH ₂) ₃		
13.				-	0	(CH ₂) ₄		
14.				-	0	(CH ₂) ₄		
15.				-	0	(CH ₂) ₄		

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
16.			-	O	(CH ₂) ₄	CO ₂ Butyl ^t		
17.			-	O	CH ₂ CO	H		
18.			-	O	CH ₂ CO	H		
19.			-	O	(CH ₂) ₂ CO	H		
20.			-	O	(CH ₂) ₂ CO	H		
21.			-	O	CH ₂ CO	H		
22.			-	-		H		
23.			-	-		H		
24.			-	-		H		

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
25.			OH	-	-	-	H	
26.			OH	-	-	-	H	
27.			OH	-	-	-	H	
28.			OH	-	-	-	H	
29.			OH	-	-	-	H	
30.			OH	-	-	-	H	
31.			OH	-	-	-	H	
32.			OH	-	-	-	Methyl	
33.			OH	-	-	-	H	Ethyl

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
34.			OH	-	-	-	H	1-Propyl
35.			OH	-	-	-	H	2-Propargyl
36.			OH	-	-	-	H	2-Propenyl
37.			OH	-	-	-	H	2-Propyl
38.			OH	-	-	-	H	Cyclopropyl
39.			OH	-	-	-	H	1-Butyl
40.			OH	-	-	-	H	
41.			OH	-	-	-	H	
42.			OH	-	-	-	H	

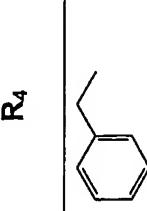
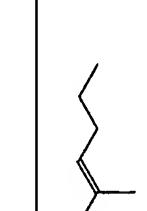
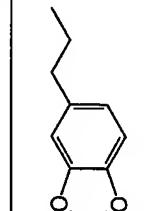
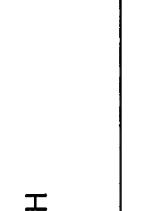
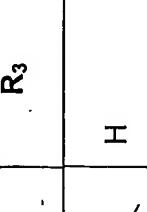
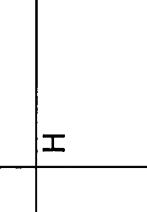
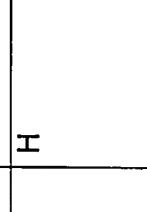
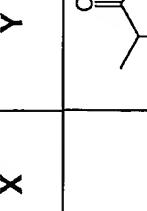
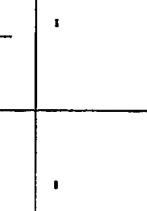
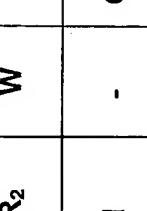
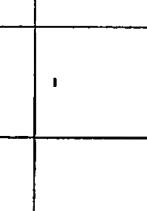
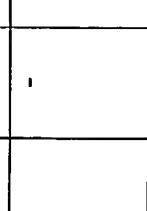
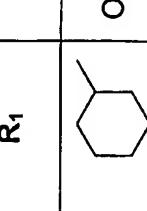
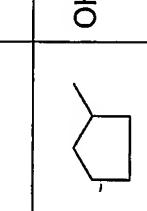
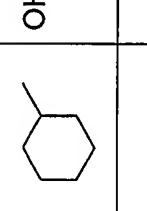
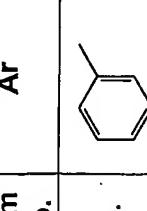
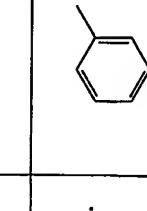
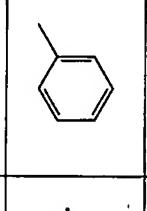
Com No.	Ar	R ₁	R ₂	W	X	Y	-	R ₃	R ₄
43.			OH	-	-	-	H		
44.			OH	-	-	-	H		
45.			OH	-	-	-	H		
46.			OH	-	-	-	H		
47.			OH	-	-	-	H		
48.			OH	-	-	-	H		
49.			OH	-	-	-	H		

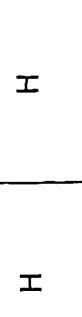
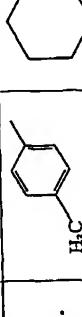
Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
50.			OH	-	-	-	H	
51.			OH	-	-	-	H	
52.			OH	-	-	-	H	
53.			OH	-	-	-	H	
54.			OH	-	-	-	H	
55.			OH	-	-	-	H	
56.			OH	-	-	-	H	

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
57.			OH	-	-	-	H	
58.			OH	-	-	-	H	
59.			OMe	-	-	-	H	
60.			OMe	-	-	-	Ethy	
61.					-	-	H	
62.			OMe	-	-	-	H	
63.			OMe	-	-	-	H	
64.					-	-	H	

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
65.			OH	-	-	-	H	
66.			OH	-	-	-	H	
67.			OH	-	-	-	H	
68.			OH	-	-	-	H	
69.			OH	-	-	-	H	
70			OH	-	-	-	H	
71.			OH	-	-	-	H	

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
72.			OH	-	-	-	H	
73.			OH	-	-	-	H	
74.			OH	-	NH			
75.			OH	-	NH			
76.			OH	-	NH			
77.			OH	-	-			
78.			OH	-	NH			
79.			OH	-	NH			

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
80.			OH	-	O		H	
81.			OH	-	-	-	H	
82.			OH	-	-	-	H	
85.			OH	-	-	-	H	
86.			F	-	OH	-	H	
87.			H ₃ CO	-	OH	-	H	

Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
88.			OH	-	-	-	H	H
89.			OH	-	-	-	H	H
90.			OH	-	-	-	H	H
91.			OH	-	-	-	H	H
92.			OH	-	-	-	H	H
93.			OH	-	O	-CH ₂ CO-	H	H



Com No.	Ar	R ₁	R ₂	W	X	Y	R ₃	R ₄
94.			OH	-	O	-CH(CH ₃)CO-	H	H
95.			OH	-	O	-(CH ₂) ₄ -	CO ₂ C(CH ₃) ₃	H
96.			O(CH ₂) ₂ CH ₃	-	O	(CH ₂) ₄ -	-CO ₂ C(CH ₃) ₃	H
97.					-	-	H	H
98.					-	-	H	H

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation for the particular compounds. The examples are given to illustrate particular aspects of the disclosure and should not be constrained to limit the scope of the invention as defined by the claims.

5

EXPERIMENTAL DETAILS

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, and dichloromethane, were dried using various drying reagents according to the procedures well known in the literature. IR spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon instrument, Nuclear Magnetic

10 Resonance (NMR) were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

Example 1

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-diphenyl acetamide (Compound No.1).

15 **Step a:** Preparation of 2-hydroxy-2,2-diphenyl acetic acid : Synthesized as per reported procedure in Vogel's Textbook of Practical Organic Chemistry, page 1046 (5th Ed).

Step b: Preparation of ($1\alpha,5\alpha,6\alpha$)-3N-benzyl-6-amino-3-azabicyclo[3.1.0]hexane :

20 Synthesized as per reported procedure of Braish, T.F. et.al. *Syn. Lett.* 1100(1996).

Step c: To a solution of ($1\alpha,5\alpha,6\alpha$)-3N-benzyl-6-amino-3-azabicyclo[3.1.0] hexane (1mmol, 0.188 gm) in DMF (5 ml) was added 2-hydroxy-2,2-diphenyl acetic acid (1 mmol, 0.225 gm) and cooled to 0°C. The reaction mixture was treated with hydroxy benzotriazole (1 mmol, 0.135 g) followed by N-methyl morpholine (2 mmol, 0.202

25 gm) and stirred at 0°C for 0.5 hrs. It was followed by the addition of EDC (1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride, (1mmol. 0.192 gms). The reaction mixture (RM) after stirring at 0°C for 1 hr. was later stirred at room temperature overnight. The RM was then poured into cold water and extracted with ethyl acetate. The combined organic layers were washed with water and dried over sodium sulphate. The crude compound obtained after removing the solvent was

purified by column chromatography (silicagel 100-200 mesh), eluting the compound with 30-70, ethyl acetate-hexane mixture.

m.p.:172°C

5 $^1\text{H-NMR}$ (CDCl_3) δ -7.39 - 6.29 (m, arom, 10H), 3.58 (s, 2H, benzylic), 3.14 - 3.07 (m, 3H, piperazine protons & α - hydrogen), 2.38-2.35 (d, 2H, piperazine protons), d 1.42 (d, 2H, cyclopropyl).

IR (K Br) : 1657 cm⁻¹ (amide carbonyl).

Example 2

10 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(4-fluorophenyl) acetamide (Compound No.2).**

This compound was synthesized following the procedure as described in Example 1 using 4-fluorobenzaldehyde instead of benzaldehyde in step a of Example 1 to obtain the corresponding 2-hydroxy-2,2-di(4-fluorophenyl) acetic acid.

15 $^1\text{H-NMR}$ (CDCl_3) 7.46-6.93 (m, 13H, arom), 3.58 (s, 2H, benzylic), 3.18 (t, 3H, piperazine protons & α - hydrogen), 2.45 (d, 2H, piperazine protons), d 1.5 (s, 2H, cyclopropyl).

IR: 1658 cm⁻¹ (amide carbonyl).

Example 3

20 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenoxy)-2,2-diphenyl acetamide (Compound No.3)**

Step a: Preparation of 2-allyloxy 2,2-diphenyl acetic acid :

(i) Preparation of ethyl 2-allyloxy-2,2-diphenyl acetate:

A solution of ethyl-2-hydroxy-2,2-diphenyl acetate (1 mmol, 0.256 gm) in N,N-dimethylformamide (DMF) (5 ml) was added to a suspension of sodium hydride (1.2 mmol) in DMF at 0°C. The reaction mixture was stirred at room temperature for 1 hr., then cooled to 0°C and allyl bromide (1mmol, 0.117 gm) diluted with 0.5 ml of DMF was added to the reaction mixture and stirred at room temperature for 2 hrs. The reaction was quenched by the addition of a concentrated aqueous solution of

ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over sodium sulphate. The crude compound obtained on evaporation of the solvents was purified by column chromatography (silica gel 100-200 mesh), eluting the compound with 0.5-9.5 ethyl 5 acetate -hexane mixture.

¹H-NMR : (CDCl₃, δ) : 7.52 – 7.3 (m, 10H, arom.), 5.36 – 5.14 (m, 2H, vinylic), 4.72 – 4.7 (d, 2H, OCH₂), 4.29 – 4.27 (q, 2H, OCH₂), 1.3-1.22(t, 3H, CH₃).

IR (DCM) : 1738 cm⁻¹ (ester carbonyl)

(ii) Preparation of 2-allyloxy-2,2-diphenyl acetic acid :

10 A solution of ethyl-2-allyloxy-2,2-diphenyl acetate (1mmol, 0.292 gm) in methanol (5 ml) was added to a solution of potassium hydroxide (2 mmol, 0.112 gms), in 2 ml of water and stirred at room temperature overnight. The organic solvents were removed from the reaction mixture by evaporation and the reaction mixture was acidified with dilute hydrochloric acid to pH-3. The compound was extracted with 15 ethyl acetate. The combined organic layers were washed with water, brine and dried over anhydrous sodium sulphate. The solvent was removed completely to give the title compound in 88% yield, m.p. 125°C.

¹H-NMR (CDCl₃, δ) : 7.48-7.25 (m, 10H, arom.), 5.93-5.84(m, 1H, vinylic), 5.32-5.17 (vinyllic protons).

20 IR (KBr): 1713cm⁻¹ (acid carbonyl).

Step b: Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenoxy)-2,2-diphenyl acetamide

To a solution of 6-amino-3-azabicyclo [3.1.0]hexane (1mmol, 0.188 gm) in DMF (5 ml) was added 2-allyloxy-2,2-diphenyl acetic acid (1 mmol., 0.266 gm). The reaction 25 mixture was cooled to 0°C, and was treated with hydroxy benzotriazole (1 mmol, 0.135 g), followed by the addition of N-methyl morpholine (2 mmol, 0.202 gm) and maintained at 0°C for 0.5 hrs. It was then followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl)carbodiimide hydrochloride, (1mmol, 0.192 gm). The reaction mixture after stirring at 0°C for 1 hr. was stirred at room temperature

overnight. The reaction mixture was poured into cold water and extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over sodium sulphate. The crude compound obtained on evaporation of the solvents was purified by column chromatography (silicagel, 100-200 mesh), eluting the compound
 5 with 30-70, ethyl acetate-hexane mixture.

¹H-NMR (CDCl₃, δ- values) ; 7.46-7.09 (m, arom, 15H), 5.84 (m, 1H, allylic), 5.3 - 5.14 (dd, 2H, allylic) 3.57 -3.53 (m, 4H, -N-CH₂ & O-CH₂) 3.1 - 3.06 (m, 3H, α-hydrogen and piperazine protons), 2.38 - 2.35 (d, 2H, piperazine protons).

IR (DCM) : 1682 cm⁻¹ (amide carbonyl).

10

Example 4

Preparation of (1α,5α,6α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenoxy)-2,2-di(4-fluorophenyl) acetamide. (Compound No.4)

This was synthesized following the procedure as in Example 3 but starting from the corresponding fluoro derivative. m.p. 93-95°C.

15

¹H-NMR (CDCl₃) ; 7.43-6.98 (m, arom, 13H), 5.8 (m, 1H, allylic), 5.2(m, 2H, allylic), 3.5 (d, 4H, -N-CH₂ & O-CH₂), 3.06 (d, 3H, α-hydrogen and piperazine protons), 2.36 (d, 2H, piperazine protons).

IR (KBr) : 1670 cm⁻¹ (amide carbonyl).

Example 5

20

Preparation of (1α,5α,6α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-propyloxy-2,2-diphenyl acetamide (Compound No.5)

This was synthesized following the procedure as in Example 3 using n-propyl bromide instead of allyl bromide in step a.

25

¹H-NMR(CDCl₃): 7.4 -7.09 (m, 15H, arom), 3.53 (s, 2H, benzylic), 3.09 - 3.068 (m, 3H, α-hydrogen & piperazine protons).

IR (DCM) : 1666 cm⁻¹ (amide carbonyl)

Example 6

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-propyloxy-2,2-di(4-fluoro phenyl) acetamide (Compound No.6).

This was synthesized following the procedure as in Example 3 using the
5 corresponding fluoro derivative. m.p. 110°C.

$^1\text{H-NMR}$ (CDCl_3): 7.4 –6.97 (m, 13H, arom), 3.54 (s, 2H, benzylic), 3.08 (d, 3H, α -hydrogen & piperazine protons), 2.92(t, 2H, piperazine), 2.37 (d, 2H), 1.56 (m, 4H), 0.9 (t, 3H, methyl).

IR (KBr) : 1659 cm^{-1} (amide carbonyl)

10

Example 7

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propynyl)-2,2-diphenyl acetamide (Compound No. 7).

This was synthesized following the procedure as described in Example 3 but using propargyl bromide instead of allyl bromide in step a.

15 $^1\text{H-NMR}$ (CDCl_3) : 7.48 - 7.2 (m, 15H, arom.), 3.73 (s, 2H, OCH_2), 3.56(s, 2H, N- CH_2), 3.12 – 3.09(m, 3H, α -hydrogen & piperazine protons) 2.44-2.39 (m, 3H, piperazine protons & acetylene protons).

IR (DCM) : 1680 cm^{-1} (amide carbonyl)

Example 8

20 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(2-furyl) acetamide (Compound No.8)**

Step a: Synthesis of 2-hydroxy-2,2-di(2-furyl) acetic acid : Synthesized as per reported procedure in Vogel's Text Book of Practical Organic Chemistry, page 1048 (5th ed).

25 **Step b:** The compound was synthesized following the procedure given in step c of Example 1 using 2-hydroxy-2,2-di(2-furyl) acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

¹H-NMR (CDCl₃) 7.38-6.29 (m, 11H, arom), 3.58 (s, 2H, bezylic), 3.15 (m, 3H, α -hydrogen & piperazine protons), 2.44-2.41 (m, 2H, piperazine protons), 1.65-1.6(m, 3H, cyclopropyl).

IR (KBr) : 1641 cm⁻¹(amide carbonyl).

5

Example 9

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(2-thienyl) acetamide (Compound No.9).

Step a: Synthesis of 2-hydroxy-2,2-di(2-thienyl) acetic acid :

Synthesized as per reported procedure in Vogel's Text Book of Practical Organic
10 Chemistry, page 1048 (5th ed)

Step b: The compound No.9 was synthesized following the procedure given in step c of Example 1 using 2-hydroxy-2,2-di(2-thienyl) acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

¹H-NMR (CDCl₃); 7.33-6.93 (m, 6H), 6.33 (s, OH), 3.58 (s, 1H), 3.13-3.10 (m, 1H),
15 2.43-2.40 (m, 2H), 2.06-2.02 (m, 2H), 1.68 (bm), 1.34-1.24 (m, 2H), 0.90-0.87 (m, 1H).

IR (DCM) :1660Cm⁻¹

Example 10

Preparation of (1 α ,5 α ,6 α)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyoxy carbonylbutyl-1-(2-hydroxy-2,2-diphenyl)acetate (Compound No.10)

Step a: Preparation of 6-[N- α -bromobutyl, N-tert-butyloxycarbonyl, N-3-benzyl-3-azabicyclo[3.1.0]hexane] : A solution of 6-N-tert-butyloxy carbonyl, N-3-benzyl-3-azabicyclo[3.1.0]hexane (1mmol) in N,N-dimethylformamide (DMF) (5 ml) was added to a cold suspension of sodium hydride in DMF under nitrogen. The reaction mixture was stirred at room temperature for 1 hr., cooled to 0°C and to it was added a solution of 1,4-dibromobutane (2mmol) in DMF. The reaction mixture was stirred at room temperature for 3 hrs., quenched the reaction mixture by the addition of aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over sodium

sulphate. The crude compound obtained on evaporation of the solvents was purified by column chromatography (silica gel 100-200 mesh), eluting the compound with 25-75, ethyl acetate-hexane mixture.

5 $^1\text{H-NMR}$ (CDCl_3) 7.33-7.24 (m, 5H, arom.) , 3.59 (s, 2H, methylene) , 3.46-3.42 (t, 2H, N- CH_2), 3.24 –3.19 & 3.08-3.05 (d's, 4H, piperazine protons) 2.82 (s, 1H, α -proton), 2.46-2.44 (t,2H, $\text{CH}_2\text{-Br}$).

IR (DCM) : 1683 cm^{-1} (carbamate).

10 **Step b:** To a solution of 2-hydroxy-2,2-diphenyl acetic acid (1mmol, 0.228gms) in xylene was added, 6-[N- α -bromobutyl, N-tert-butyloxycarbonyl, N-3-benzyl-3-azabicyclo [3.1.0]hexane] (1mmol, 0.423gms) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 2mmol, 0.305 gms) and refluxed the reaction mixture for 6 hrs. The reaction mixture was washed with water, brine and dried over sodium sulphate. The solvents were evaporated and the crude compound thus obtained was purified by column chromatography (silicagel, 100-200 mesh), eluting the compound with 20-80, 15 ethyl acetate-hexane mixture.

15 $^1\text{H-NMR}$ (CDCl_3) ; 7.41 to 7.26 (m, 15 H, arom), 4.27 (t, 2H, ester- CH_2) 3.57 (s, 2H, benzylic).

IR (DCM) : 1688 cm^{-1} (carbamate), 1725 cm^{-1} (ester carbonyl)

Example 11

20 Preparation of ($1\alpha,5\alpha,6\alpha$)-3-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyoxy carbonylpropyl-1-(2-hydroxy-2,2-diphenyl)acetate (Compound No.11)

This compound was synthesized following the procedure of Example 10 by using 1,3-dibromopropane in step a instead of 1,4-dibromobutane.

25 $^1\text{H-NMR}$ (CDCl_3 , δ -values) : 7.4 - 7.25 (m, 15H, arom), 4.34 - 4.24 (2H, t, ester- CH_2), 2.95 - 2.93(d, 2H, piperazine protons), 2.74(s, 1H, α -proton), 2.36 to 2.33 (d, 2H, piperazine protons).

IR (DCM) : 1731 cm^{-1} (carbamate), 1688 cm^{-1} (amide carbonyl)

Example 12

Preparation of ($1\alpha,5\alpha,6\alpha$)-3-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonyl propyl-1-(2-propyloxy-2,2-diphenyl) acetate (Compound No.12).

5 This compound was synthesized following the procedure of Example 10 by reacting 2-propyloxy-2,2-diphenyl acetic acid as obtained in Example 5 and 6-[N- α -bromopropyl, N-tert-butyloxycarbonyl, N-3-benzyl-3-azabicyclo [3.1.0]hexane].

10 $^1\text{H-NMR}$ (CDCl_3) : 7.44-7.22 (m, 15H, arom), 4.18-4.14 (t, 2H, ester - CH_2 -), 3.54 (s, 2H, benzylic) 3.2-3.16 (t, 2H, - OCH_2), 3.11-3.06 (t, 2H, N- CH_2), 2.97-2.94 (d, 2H, piperazine protons), 2.75 (s, 1H, α -hydrogen), 2.37-2.34 (d, 2H, piperazine protons).

IR (DCM): 1735 cm^{-1} (carbamate), 1689 cm^{-1} (amide carbonyl)

Example 13

15 **Preparation of ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonylbutyl-1-(2-propyloxy-2,2-diphenyl)acetate (Compound No.13)**

This compound was synthesized following the procedure of Example 10 by reacting 2-propyloxy-2,2-diphenyl acetic acid as obtained in Example 5 and 6-[N- α -bromobutyl, N-tert-butyloxycarbonyl, N-3-benzyl-3-azabicyclo [3.1.0]hexane].

20 $^1\text{H-NMR}$ (CDCl_3) : 7.45 -7.25 (m, 15H, arom), 4.18 - 4.14 (t, 2H, ester, - CH_2 -) 3.56 (s, 2H, benzylic protons), 3.2 - 3.15 (t, 2H, OCH_2), 3.11-3.07 (t, 2H, N- CH_2), 3.2-3.15 (t, 2H, OCH_2), 3.11-3.07 (t, 2H, N- CH_2), 3.2-2.99 (d, 2H, piperazine protons); 2.73 (s, 1H, α -proton), 2.42-2.39 (d, 2H, piperazine protons).

IR (DCM) : 1733 cm^{-1} (carbamate), 1687 $^{-1}$ (amide carbonyl).

Example 14

25 **Preparation of ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonyl butyl-1-(2-(2-propenyloxy)-2,2-diphenyl) acetate (Compound No.14)**

This compound was synthesized following the procedure as described in Example 10 by reacting 2-(2-propenyloxy)-2,2-diphenyl acetic acid as obtained in

Example 3 and 6-[N-*α*-bromobutyl, N-tert-butyloxycarbonyl, N-3-benzyl-3-azabicyclo[3.1.0]hexane].

¹H-NMR (CDCl₃) :7.45-7.25(m, 15H, arom), 5.31-5.12(d, d, 2H, vinyl), 4.19-4.15 (t, 2H, ester,-CH₂), 3.81-3.79 (2H, t-CH₂); 3.56 (s, 2H, benzylic)

5 IR (DCM) : 1736 cm⁻¹ (carbamate), 1689 cm⁻¹ (amide carbonyl)

Example 15

Preparation of (1*α*,5*α*,6*α*)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonylbutyl-1-(2-hydroxy-2,2-di(4-fluorophenyl))acetate (Compound No.15)

10 This compound was synthesized following the procedure of Example 10 by using 2-hydroxy-2,2-di(4-fluorophenyl) acetic acid as obtained in Example 2.

¹H-NMR (CDCl₃) :7.4-6.98(m, 13H, arom), 4.29-4.24 (t, 2H, ester,-CH₂), 3.56 (s, 2H, benzylic), 3.15-3.1 (t, 2H, N-CH₂), 3.02-2.98 (m, 2H, piperazine), 2.73 (m, 1H, *α*-hydrogen), 2.42-2.39(m, 2H, piperazine)

15 IR (DCM) : 1731 cm⁻¹ (carbamate), 1686 cm⁻¹ (amide carbonyl)

Example 16

Preparation of (1*α*,5*α*,6*α*)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxycarbonyl butyl-1-(2-propyloxy-2,2-di(4-fluorophenyl)) acetate (Compound No.16)

20 The title compound was synthesized following the procedure described in Example 10 using 2-propyloxy-2,2-di(4-fluorophenyl) acetic acid as obtained in Example 6.

25 ¹H-NMR (CDCl₃) :7.43 –6.98 (m, 13H, arom), 4.2 - 4.15 (t, 2H, ester, -CH₂-) 3.58 (s, 2H, benzylic protons), 3.2 - 3.11 (m, 2H, OCH₂ & N-CH₂), 3.05-3.018 (d, 2H, piperazine protons); 2.76 (s, 1H, *α*-proton), 2.42-2.39 (d, 2H, piperazine protons).

IR (DCM) : 1735 cm⁻¹ (carbamate), 1692 cm⁻¹ (amide carbonyl).

Example 17

Preparation of ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido-2-(2-propyloxy)-2,2-diphenyl acetate (Compound No.17).

Step a : Preparation of 6-N-chloromethylcarbonyl-3-N-benzyl-3-azabicyclo[3.1.0]

5 hexane.

To a solution of 6-amino- 3-N-benzyl-3-azabicyclo[3.1.0]hexane [1 mmol, 0.188gms] in dichloromethane at -10°C was added chloroacetyl chloride (1mmol, 0.113gms) followed by the addition triethylamine (2 mmol, 0.2gms). The reaction mixture was allowed to cool to room temperature and stirred for 1 hr. at room temperature. It was 10 washed with water, brine and dried over sodium sulphate. The solvent was evaporated to afford the title compound.

$^1\text{H-NMR}$ (CDCl_3) : 7.33 – 7.22 (m, 5H, arom.), 4.01 (s, 2H, COCH_2), 3.6 (s, 2H, NCH_2), 3.15 – 3.12 (m, 3H, α -hydrogen & piperazine protons), 2.46-2.43 (d, 2H, piperazine protons).

15 IR (DCM) : 1652 cm^{-1} (amide carbonyl).

Step b: To a solution of 2-propyloxy-2,2-diphenyl acetic acid (1mmol, 0.153gms) in xylene, was added 6-N-chloromethylcarbonyl-3-N-benzyl-3-azabicyclo[3.1.0]hexane (1mmol 0.265gms) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU, 2mmol, 0.305 gms) and the reaction mixture was refluxed for 6 hrs. The reaction mixture was

20 cooled, washed with water, brine and dried over sodium sulphate. The crude compound obtained on evaporation of the solvent was purified by column chromatography (silicagel 100-200 mesh), eluting the compound with ethylacetate-hexane, (25:75) mixture.

$^1\text{H-NMR}$ (CDCl_3): 7.48-7.23 (m, 15H, arom), 4.6 (s, 2H, ester, CH_2); 3.55 (s, 2H,

25 benzylic), 3.25-3.21 (t, 2H, OCH_2); 3.04-30.01 (d, 2H, piperazine protons), 2.88 (s, 1H, α -hydrogen).

I.R (DCM) : 1751 cm^{-1} (ester carbonyl), 1681 cm^{-1} (amide carbonyl)

Example 18

Preparation of ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido-2-(2-propenyoxy)-2,2-diphenyl acetate (Compound No.18).

The title compound was synthesized following the procedure described in Example 17 using 2-propenyoxy-2,2-diphenyl acetic acid as obtained in Example 3 instead of 2-propyloxy-2,2-diphenyl acetic acid, and 6-N-chloromethylcarbonyl-3-N-benzyl-3-azabicyclo[3.1.0]hexane.

$^1\text{H-NMR}$ (CDCl_3) : 7.49-7.23 (m, 15H, arom.), 5.38-5.15 (m, 2H, vinylprotons); 4.64 (s, 2H, ester- CH_2), 3.85 (d, 2H, -O- CH_2); 3.55 (s, 2H, benzylic), 3.05-3.02 (d, 2H, piperazine protons), 2.89 (s, 1H, α -hydrogen).

IR (DCM) 1746.93 cm^{-1} (ester carbonyl), 1672 cm^{-1} (amide carbonyl)

Example 19

Preparation of ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-propionamido-2-(2-propenyoxy)-2,2-diphenyl acetate (Compound No.19)

The title compound was synthesized following the procedure as described in Example 17 by reacting 2-propenyoxy-2,2-diphenyl acetic acid as obtained in Example 3, with 6-N-chloromethylcarbonyl-3-N-benzyl-3-azabicyclo[3.1.0]hexane.

$^1\text{H-NMR}$ (CDCl_3) : 7.52-7.23 (m, 15H, arom), δ 5.37-5.15 (m, 2H, vinylic protons), 3.55 (s, 2H, benzylic protons)

IR (DCM) : 1746.48 cm^{-1} (ester carbonyl), 1681 cm^{-1} (amide carbonyl)

Example 20

Preparation of ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-propionamido-2-(2-propyloxy)-2,2-diphenyl acetate (Compound No.20).

The title compound was synthesized following the procedure of Example 17 by using 2-propyloxy-2,2-diphenyl acetic acid as obtained in Example 5.

$^1\text{H-NMR}$ (CDCl_3) : 7.52-7.23 (m, 15H, arom.), 5.31 (m, 1H, ester carboxyl- $\text{CH}-$); 3.55 (s, 2H, benzylic).

IR (DCM) : 1746.48 cm^{-1} (ester carbonyl), 1681 cm^{-1} (amide carbonyl)

Example 21

Preparation of (1 α ,5 α ,6 α)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido-2-hydroxy-2,2-di(4-fluorophenyl) acetate (Compound No.21)

The title compound was synthesized following the procedure as described in
 5 Example 17 by using 2-hydroxy-2,2-di(4-fluorophenyl) acetic acid as obtained in
 Example 2.

$^1\text{H-NMR}$ (CDCl_3) 7.41-7.04 (m, 13H, arom), 4.67(s, 2H, O- CH_2), 3.54(s, 2H, N- CH_2),
 3.05-3.02(d, 2H, piperazine), 2.92 (m, 1H, α -hydrogen), 2.36-2.33(d, 2H, piperazine).

IR (DCM) : 1745 cm^{-1} (ester carbonyl), 1664 cm^{-1} (amide carbonyl)

10

Example 22

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.22).

Step a: Synthesis of 2-hydroxy-2-cyclohexyl phenyl acetic acid:

This was prepared following the procedure as described in J. Amer. Chem. Soc. 75,
 15 2654 (1953).

Step b: Synthesis of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide.

The compound of step b was prepared following the procedure as described in
 step c of Example 1 using 2-hydroxy-2-cyclohexyl phenyl acetic acid instead of 2-
 20 hydroxy-2,2-diphenyl acetic acid.

$^1\text{H-NMR}$: (CDCl_3) 7.83-7.26 (m, 10H), 4.29-4.25 (t, 4H), 2.16-2.12 (q, 2H)

I.R. (DCM) : 1690 cm^{-1}

Example 23

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,5-difluoro benzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.23).

The compound obtained in Example 22 was debenzylated and then N-alkylated as given below:

Step a: A solution of 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-phenyl acetamide (1mmol) in methanol (50 ml) was added to a suspension of Pd/C (10%, 0.1 gm) and the reaction mixture was hydrogenated in Parr apparatus at 45 psi for 3hrs. The reaction mixture was filtered and concentrated to afford the title compound.

5 ¹H-NMR (CDCl₃): 7.47-6.74 (m, 5H, arom.), 3.24-3.16 (m, 3H, piperazine protons & α -proton), 3.07 –3.02 (m, 2H, piperazine protons),

IR (DCM) : 1660 cm⁻¹ (amide carbonyl)

Step b: To a solution of 6-N-(3-azabicyclo[3.1.0]cyclohexyl)-2-hydroxy-2-cyclohexyl-2-phenyl acetamide (1 mmol 0.328gms) in DMF (5 ml) was added potassium carbonate (2mmol 0.276gms), potassium iodide (1mmol 0.166gms) and 3,5-difluoro benzyl bromide (1.2 mmol 0.2gms). The reaction mixture was stirred at room temperature overnight, poured into water and extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over sodium sulphate. The crude compound obtained after evaporation of the solvent under vacuum was purified by column chromatography (silica gel 100-200 mesh), eluting the compound with ethyl acetate.

10 ¹H-NMR(CDCl₃) 7.59-6.6 (m, 8H, arom.), 4.07 (s, 2H, N-CH₂); 3.49-3.47(m, 3H, piperazine & α -hydrogen).

15 20 IR (DCM) : 1655 cm⁻¹ (amide carbonyl)

Example 24

Preparation (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-bromobenzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.24).

This compound was synthesized following the procedure as in Example 23
25 but using 4-bromobenzyl bromide instead of 3,5-difluoro benzyl bromide.

¹H-NMR(CDCl₃) 7.72-7.2 (m, 9H, arom.), 3.61(s, 2H, N-CH₂); 3.18-3.09(m, 3H, piperazine & α -hydrogen), 2.48-2.45(m, 2H, piperazine).

IR (DCM) : 1658 cm⁻¹ (amide carbonyl)

Example 25**Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2,6-difluoro benzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.25).**

The title compound was synthesized following the procedure as described in
 5 Example 23 using 2,6-difluorobenzyl bromide instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.59-6.82 (m, 8H, arom.), 3.73(s, 2H, N-CH₂); 3.06-3.01(m, 2H, piperazine) 2.89(1H, m, α -hydrogen), 2.48-2.45(m, 2H, piperazine).

IR (DCM) : 1635 cm⁻¹ (amide carbonyl)

Example 26**10 Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylbenzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.26)**

The title compound was synthesized following the procedure as described in
 Example 23 using 2-bromomethyl biphenyl instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.59-7.21 (m, 14H, arom.), 3.44(s, 2H, N-CH₂); 3.028-2.95 (m, 2H, piperazine) 2.87 (1H, m, α -hydrogen), 2.26-2.25 (m, 2H, piperazine).

IR (DCM) : 1659 cm⁻¹ (amide carbonyl)

Example 27**Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.27).**

20 The compound obtained in step a of Example 23 (300mg; 1mmol) was dissolved in acetonitrile (20 ml) and potassium carbonate (1.5mmol), potassium iodide (catalytical amount) were added to it at room temperature. It was followed by the addition of 2-phenyl ethyl bromide to the reaction mixture and was stirred at reflux for 8 hrs. The reaction mixture was filtered and the filtrate was taken in ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulphate. It was concentrated under reduced pressure and purified over silica gel
 25 (100-200 mesh) using ethyl acetate/hexane mixture.

$^1\text{H-NMR}(\text{CDCl}_3 \delta - \text{values})$ 7.59-7.1 (m, 9H, arom.), 3.15 (t, 2H, N-CH₂- C); 2.67 – 2.59 (m, 3H, piperazine & α -hydrogen), 2.38 -2.24 (m, 2H, piperazine).

IR (DCM) : 1652 cm⁻¹ (amide carbonyl)

Example 28

5 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(2,3-dihydro benzofuran-5-yl)ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.28).**

Step a: Synthesis of 5-(2-bromoethyl)-2,,3-dihydrobenzofuran.

The title compound was synthesized following the procedure as given in EP132130 and EP0388054.

10 **Step b:** The title compound No.28 was synthesized by using 5-(2-bromoethyl) 2,3-dihydrobenzofuran following the procedure described in Example 27.

¹H-NMR(CDCl₃) 7.59-6.6 (m, 8H, arom.), 5.54 (t, 2H, N-CH₂- C); 2.59 – 2.55 (m, 3H, piperazine & α -hydrogen), 2.38 -2.34 (m, 2H, piperazine).

IR (DCM) : 1651 cm⁻¹ (amide carbonyl)

Example 29

15 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(3,4-methylenedioxyphenyl)ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.29).**

Step a: Synthesis of 3,4-methylenedioxymethyl bromide.

This compound was synthesized following the procedure as given in EP132130 and EP0388054.

Step b: Compound No. 29 was synthesized following the procedure as described in Example 27 using 3,4-methylenedioxymethyl bromide.

25 ¹H-NMR(CDCl₃) 7.59-6.56 (m, 8H, arom.), 5.89 (s, 2H, methylenedioxy) 3.15 (t, 2H, N-CH₂- C); 2.58 – 2.55 (m, 3H, piperazine & α -hydrogen), 2.38 -2.34 (m, 2H, piperazine).

IR (DCM) : 1653 cm⁻¹ (amide carbonyl)

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-(2,3-dihydrobenzofuran-5-yl)acetyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.30).

Step a: Synthesis of 5-chloroacetyl-2,3-dihydrobenzofuran.

5 This compound was synthesized following the procedure as given in EP0388054.

Step b: Compound No.30 was synthesized following the procedure as given in Example 27 using 5-chloroacetyl-2,3-dihydrobenzofuran.

10 $^1\text{H-NMR}(\text{CDCl}_3)$ 7.59-6.6 (m, 8H, arom.), 4.15 (t, 2H, N-CH₂- C); 3.17 – 3.11 (m, 2H, piperazine) 2.85 (m, 1H, α -hydrogen), 2.38 -2.34 (m, 2H, piperazine).

IR (DCM) : 1651 cm⁻¹ (amide carbonyl)

Example 31

Prepartion of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(benzofuran-5-yl)ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.31)

15 **Step a:** Synthesis of 5-(2-bromoethyl)benzo[2,3-b]furan.

This compound was synthesized following the procedure as given in EP132130 and EP0388054.

Step b: This was synthesized following the procedure as in Example 27 using 5-(2-bromoethyl)benzo[2,3-b]furan instead of 2-phenyl ethyl bromide.

20 $^1\text{H-NMR}(\text{CDCl}_3)$ 7.59-6.59 (m, 9H, arom.), 3.18 (t, 2H, N-CH₂- C); 2.76 – 2.73 (m, 3H, piperazine & α -hydrogen), 2.38 -2.34 (m, 2H, piperazine).

IR (DCM) : 1649 cm⁻¹ (amide carbonyl)

Example 32

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-methyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.32).

This compound was synthesized following the procedure as described in step b of Example 23 using methyl iodide instead of 3,5-difluoro benzyl bromide.

¹H-NMR (CDCl₃) 7.6 – 7.19 (m, 5H, aromatic) 3.64 (s, 3H, N-CH₃) , 3.4 (m, 1H, α -hydrogen) 3.37 to 2.87 (m, 4H, piperazine protons) , 2.39 (m, 1H) 1.77 to 0.91 (m, 10H, aliphatic , cyclohexyl), 0.8 (m, 2H, cyclopropyl)

I.R.(DCM) :1656 cm⁻¹

5

Example 33

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-ethyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.33).

This compound was synthesized following the procedure as described in step b of Example 23 using iodoethane instead of 3,5-difluoro benzyl bromide.

10 ¹H-NMR(CDCl₃) 7.6 – 7.22 (m, 5H, aromatic) 3.16 (q, 2H, N-CH₂) , 2.88 (m, 1H, α -hydrogen) 2.46 to 2.38 (m, 4H, piperazine protons) , 2.1 (m, 1H) 1.77 to 1.2 (m, 10H, aliphatic , cyclohexyl), 1.05 (t, 3H –CH₃) 0.8 (m, 2H, cyclopropyl)

I.R.(DCM) :1657 cm⁻¹

Example 34

15 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-propyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.34).**

This compound was synthesized following the procedure as described in step b of Example 23 but using n-propyl bromide instead of 3,5-difluoro benzyl bromide.

20 M.P. :78°C

¹H-NMR(CDCl₃) 7.64 – 7.27 (m, 5H, aromatic) 4.02 to 3.74 (m, 2H, N-CH₂) , 2.88 (m, 1H, α -hydrogen) 2.46 to 2.38 (m, 4H, piperazine protons) , 2.1 (m, 1H) 1.77 to 1.2 (m, 14H, aliphatic , cyclo hexyl & CH₂-CH₂), 1.05 (t, 3H –CH₃) 0.8 (m, 2H, cyclopropyl)

25 I.R.(DCM) :1655 cm⁻¹

Example 35

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propargyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.35).

This compound was synthesized following the procedure as in Example 23
5 using propargyl bromide instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.59 – 7.22 (m,5H, aromatic) 3.12 to 2.86 (m , 3H, α -hydrogen & piperazine protons) 2.41 to 2.35 (m, 2H, piperazine protons) , 1.77 to 1.2 (m, 9H, aliphatic , cyclo hexyl), 0.96 (m, 6H –2xCH₃) 0.8 (m, 2H, cyclopropyl)

I.R.(DCM) :1656 cm⁻¹

10

Example 36

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.36).

This compound was synthesized following the procedure as described in Example 23 using allyl bromide instead of 3,5-difluoro benzyl bromide.

15

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.6 – 7.24 (m,5H, aromatic) 5.86 to 5.11 (m, 3H, vinylic protons) 3.21 to 3.13 (m , 3H, α -hydrogen & piperazine protons) , 2.97 (m, 2H, N-CH₂) 2.41 to 2.35 (m, 2H, piperazine protons) , 1.77 to 1.2 (m, 9H, aliphatic , cyclohexyl), 0.8 (m, 2H, cyclopropyl)

I.R.(KBr) :1653 cm⁻¹

20

Example 37

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.37).

This compound was synthesized following the procedure as in Example 23 using propyl bromide instead of 3,5-difluoro benzyl bromide.

25

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.65 – 7.22 (m,5H, aromatic) 4.73. (s, 1H) 4.24 (m, 2H, N-CH₂) 3.21 to 3.13 (m , 3H, α -hydrogen & piperazine protons) 2.41 to 2.35 (m, 2H, piperazine protons) , 1.77 to 1.2 (m, 9H, aliphatic , cyclo hexyl), 0.8 (m, 2H, cyclopropyl)

I.R.(DCM) :1656cm⁻¹

Example 38

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-cyclopropyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.38).

5 This compound was synthesized following the procedure as described in Example 23 but using cyclopropyl bromide instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.62 – 7.22 (m,5H, aromatic) 3.21 to 3.15 (m, 2H, 2x α -hydrogen) 2.74 to 2.66 (m , 3H, piperazine protons) 1.77 to 0.88 (m, 9H, aliphatic , cyclo hexyl), 0.8 (m, 2H, cyclopropyl)

10 I.R.(DCM) :1660cm⁻¹

Example 39

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-butyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.39).

This compound was synthesized following the procedure as described in 15 Example 23 using n-butyl bromide instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.61 – 7.23 (m,5H, aromatic) 3.24 (m, 2H, N-CH₂) 2.52 to 2.47 (m , 5H, α -hydrogen & piperazine protons) 1.69 to 1.15 (m, 13H, aliphatic , cyclo hexyl), 0.88 (m, 5H, cyclopropyl & CH₃)

I.R.(DCM) :1664cm⁻¹

20 **Example 40**

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3-methyl-2-butenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.40).

This compound was synthesized following the procedure as in Example 23 using isoprenyl bromide instead of 3,5-difluoro benzyl bromide.

25 $^1\text{H-NMR}(\text{CDCl}_3)$ 7.77 – 7.25 (m,5H, aromatic) 5.24 (m, 1H, vinylic) 4.04 to 3.96 (m, 2H, N-CH₂) 3.83 to 3.35 (m , 5H, α -hydrogen & piperazine protons) 2.47 to 1.22 (m, 17H, aliphatic , cyclo hexyl), 0.88 (m, 2H, cyclopropyl)

I.R.(DCM) :1673cm⁻¹

Example 41

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound 41).

This compound was synthesized following the procedure as described in
 5 Example 23 using 5-bromo-2-methyl-2-pentene instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.59 – 7.22 (m, 5H, aromatic) 5.04 (m, 1H, vinylic) 3.12 to 3.07 (m, 2H, N- CH_2) 2.88 (m , 1H, α -hydrogen) 2.36 to 2.04 (m, 4H, piperazine protons) 2.08 to 1.18 (m, 19H, aliphatic , 2x CH_3 , cyclohexyl), 0.88 (m, 2H, cyclopropyl)
 10 I.R.(DCM) :1655cm⁻¹

Example 42

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,4-methylenedioxybenzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.42)

15 This compound was synthesized following the procedure as described in Example 23 using 3,4-methylenedioxybenzyl chloride instead of 3,5-difluoro benzyl bromide.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.58–6.60 (m, 8H, aromatic) 5.9 (s, 2H, methylene protons) 3.42 (s, 2H, N- CH_2), 3.05 to 2.88 (m , 3H, α -hydrogen & piperazine protons) 2.77 (m, 1H, α - hydrogen) 2.38 to 2.29 (m, 2H, piperazine protons) 1.76 to 1.15 (m, 10H, aliphatic cyclo hexyl), 0.88 (m, 2H, cyclopropyl)
 20 I.R.(DCM) :1669cm⁻¹

Example 43

25 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(6,6-dimethyl-2,4-heptadiynyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.43).**

Step a: Synthesis of 1-Chloro-6,6-dimethyl hepta-2,4-diyne. This compound was synthesized following the procedure as described in J. Med. Chem. (1995), 38, 3207-3216.

Step b Compound No. 43 was synthesized following the procedure as described in

Example 23 using 1-chloro-6,6-dimethyl hepta-2,4-diyne instead of 3,5-difluoro benzyl bromide.

¹H-NMR(CDCl₃) 7.59 – 7.22 (m, 5H, aromatic), 3.4 (s, 2H, N-CH₂), 2.97 to 2.82 (m, 5H, α -hydrogen & piperazine protons) 2.68 (m, 1H, α - hydrogen) 1.8 to 1.1 (m, 19H, aliphatic cyclohexyl), 0.88 (m, 2H, cyclopropyl)

I.R.(DCM) : 1666cm⁻¹

Example 44

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzoyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.44).

This compound was synthesized following the procedure as in Example 23 using benzoyl chloride.

¹H-NMR(CDCl₃) 7.57-7.22 (m, 10H, arom.), 3.65 – 3.52 – 2.55 (m, 2H, piperazine), 2.64 (α - hydrogen), 2.4 -2.36 (m, 2H, piperazine).

IR : 1667 cm⁻¹ and 1617 cm⁻¹ (amide carbonyl)

Example 45

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-formyl-fur-5-yl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.45).

This compound was synthesized following the procedure as in Example 23 using 2-formyl-5-chloromethylfuran instead of 3,5-difluoro benzyl bromide.

¹H-NMR(CDCl₃) : 9.54 (s, 1H, formyl) 7.58-7.22 (m, 5H, arom.), 7.16 & 6.34 (d, 2x1H, arom. furan) 3.7 (s, 1H N-CH₂) 3.13 – 3.08 (m, 2H, piperazine), 2.91 (α - hydrogen), 2.68 - -2.63 (m, 2H, piperazine), 2.38 (m, 1H, α -H in cyclo hexyl), 1.76 – 0.82 (m, 12H, cyclohexyl, cyclopropyl)

IR : 1724 cm⁻¹ (formyl) & 1675 cm⁻¹ (amide carbonyl)

Exmaple 46

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(aniline)thiourea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No. 46).

To a solution of 6-N-(3-azabicyclo[3.1.0]cyclohexyl)-2-hydroxy-2-cyclohexyl, 2-phenyl acetamide (1 mmol 0.328gms) in dichloromethane (10 ml), was added phenyl thiocyanate (1mmol, 0.135 gms) and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated and purified by 5 column chromatography (silicagel 100 – 200 mesh), eluting the compound with ethyl acetate – hexane mixture.

¹H-NMR (CDCl₃) 7.62 – 6.91 (m, 10H, arom.), 3.77 – 3.68 (m, 2H, piperazine), 2.59 (s, 1H, α -hydrogen), 2.42 – 2.17 (m, 2H, piperazine).

IR (DCM) :

10

Example 47

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(methyl, 4-amino-1-phenyl acetate) urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.47).

This compound was synthesized following the procedure as described in 15 Example 46, using 4-methoxy-acetylphenylisocyanate instead of phenyl thiocyanate.

¹H-NMR (CDCl₃) 7.59 – 7.14 (m, 10H, arom.), 3.66 (s, 3H, -OCH₃), 3.77 – 3.68 (m, 2H, piperazine), 2.59 (s, 1H, α -hydrogen), 2.42 – 2.17 (m, 2H, piperazine).

IR (DCM) :1736cm⁻¹ (ester carbonyl), 1650 cm⁻¹ (amide carbonyl).

Example 48

20 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-amino-1-phenyl aceticacid) urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.48).**

This compound was obtained on hydrolysis of compound 47 with sodium hydroxide.

25 ¹H-NMR (CDCl₃) 7.62 – 6.91 (m, 10H, arom.), 3.77 – 3.68 (m, 2H, piperazine), 2.59 (s, 1H, α -hydrogen), 2.42 – 2.17 (m, 2H, piperazine).

IR (DCM) :1717cm⁻¹ (acid carbonyl), 1640 cm⁻¹ (amide carbonyl).

Example 49

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methylphenyl-1-sulphonamide) urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.49).

5 This compound was synthesized following the procedure as described in Example 46 using 4-methylphenyl-1-sulphonamide cyanate instead of phenyl thiocyanate.

10 $^1\text{H-NMR}$ (CDCl_3 δ) 7.91 – 6.84 (m, 9H, arom.), 3.58 (m, 2H, piperazine), 4.13 (s, 1H, a-hydrogen), 3.39 (m, 2H, piperazine).

15 IR : 1749cm^{-1} , 1681cm^{-1} & 1667cm^{-1}

Example 50

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl) acetamide (Compound No.50).

15 **Step a:** Preparation of 2-(4-methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid. This compound was synthesized as per reported procedure in Syn. Comm. 11 (12) 943-946 (1981).

Step b: Compound No. 50 was synthesized following the method as given in step c of Example 85 using 2-(4-methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

20 m.p. : 171°C

$^1\text{H-NMR}$ (CDCl_3) : 7.45 (d, 2H, arom.), 7.25 - 7.21 (m, 5H, arom.), 7.14 – 7.11 (d, 2H, arom.), 6.55 (s, broad, 1H, –OH), 3.53 (s, 2H, methylene), 3.06 – 2.97 (m, 3H, α -H & piperazine protons).

IR (DCM) : 1656 cm^{-1} (amide carbonyl)

Example 51

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide (Compound No.51).

This compound was synthesized following the procedure as in Example 50 using 2-
5 (4-methoxyphényl)-2-cyclohexyl-2-hydroxy acetic acid instead of 2-(4-methylphenyl)-
2-cyclohexyl-2-hydroxy acetic acid.

¹H-NMR data (CDCl₃): 7.51- 7.48 (d, 2H, arom) 7.32 to 7.12 (m, 5H, arom), 6.89 -
6.86 (d, 2H, arom), 6.59 (s, broad, 1H, -OH), 3.8 (s, 3H, -OCH₃), 3.54 (s, 2H,
benzylic)

10 I.R. (DCM): 1655 cm⁻¹ (amide carbonyl).

Example 52

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-phenoxyphenyl) acetamide (Compound No.52).

This compound was synthesized following the procedure as described in Example
15 50 using 2-(4-phenoxyphenyl)-2-cyclohexyl-2-hydroxy acetic acid instead of 2-(4-
methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid.

Analytical data: m.p : 178°C

¹H-NMR data (CDCl₃) : 7.55-6.94 (m, 14H, arom), 6.64 (s, broad, 1H, hydroxyl),
3.53 (s, 2H, benzylic),

20 I.R(DCM) : 1655 cm⁻¹ (amide carbonyl)

Example 53

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide (Compound No.53).

This compound was synthesized following the procedure as described in Example
25 50 using 2-(4-fluorophenyl)-2-cyclohexyl-2-hydroxy acetic acid instead of 2-(4-
methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid.

¹H-NMR Data (CDCl₃, δ -values) : 7.63 - 7.58 (m, 2H, arom), 7.32 - 7.21 (m, 2H, arom), 7.09 - 7.023 (m, 2H, arom), 6.7 (s, broad, 1H, hydroxyl) 3.57 (s, 2H, benzylic), 3.13 - 3.04 (m, 3H, α-H & piperazine protons)

IR (DCM): 1655 cm⁻¹ (amide carbonyl)

5

Example 54

Preparation of (1α,5α,6α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclo hexyl-2-hydroxy-2-(3,4-methylenedioxophenyl) acetamide (Compound No.54).

This compound was synthesized following the procedure as described in Example 50 using 2-(3,4-methylenedioxophenyl)-2-cyclohexyl-2-hydroxy acetic acid instead of 10 2-(4-methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid.

Analytical data: m.p: 185°C

¹H-NMR data (CDCl₃) : 7.25 (m, 5H, arom), 7.03 (d, 2H, arom), 6.76 - 6.73 (d, 2H, arom), 6.56 (s, broad, 1H, hydroxyl), 5.93 (d, 2H, methylenedioxy), 3.53 (s, 2H, benzylic), 3.08 - 2.99 (m, 3H, α-hydrogen & piperazine protons), 2.37- 2.29 (m, 2H, 15 piperazine protons).

IR (DCM) : 1654 cm⁻¹ (amide carbonyl).

Example 55

Preparation of (1α,5α,6α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-tertbutylphenyl) acetamide (Compound No.55).

20 This compound was synthesized following the procedure as described in Example 50 using 2-(4-tertbutylphenyl)-2-cyclohexyl-2-hydroxy acetic acid instead of 2-(4-methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid.

Analytical data: m.p :165°C

¹H-NMR (CDCl₃) 7.48 - 7.45 (d, 2H, arom), 7.34 - 7.31 (2H, d, arom), 7.22 - 7.18 25 (m, 5H, arom), 6.58 (s, 1H, broad), 3.52 (s, 2H, benzylic), 3.07 - 2.99 (m, 3H, α-hydrogen & piperazine protons)

IR (KBr) : 1655 cm⁻¹ (amide carbonyl)

Example 56

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl) acetamide (Compound No.56).

5 The compound from Example 50 was debenzylated following the procedure as given in Example 23 to afford 6-N-(3-azabicyclo[3.1.0]cyclohexyl)-2-hydroxy-2-cyclohexyl- 2-(4-methylphenyl) acetamide. To 6-N-(3-azabicyclo[3.1.0]cyclohexyl)-2-hydroxy-2-cyclohexyl-2-(4-methylphenyl) acetamide (1 mmol 0.328gms) in DMF (5 ml), were added potassium carbonate (2mmol 0.276gms), potassium iodide (1mmol 0.166gms) and 5-bromo-2-methyl-2-pentene (1.2 mmol 0.2gms). The reaction mixture was stirred at room temperature overnight, poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over sodium sulphate. The crude compound obtained on evaporation of the solvents was purified by column chromatography (silica gel 100-200 mesh), eluting 10 the compound with ethyl acetate.

10 The reaction mixture was stirred at room temperature overnight, poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over sodium sulphate. The crude compound obtained on evaporation of the solvents was purified by column chromatography (silica gel 100-200 mesh), eluting 15 the compound with ethyl acetate.

$^1\text{H-NMR}$ (CDCl_3): 7.45 (d, 2H, arom.), 7.14-7.12 (d, 2H, arom), 5.04 (t, 1H, vinylic proton); 3.11-3.06 (t, 2H, NH_2) 2.85 (s, 1H, α -hydrogen).

IR (DCM) : 1655 cm^{-1} (amide carbonyl)

Example 57

20 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide (Compound No.57).**

This compound was synthesized following the procedure as described in Example 56 using 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-(4-methoxyphenyl) acetamide instead of 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-(4-methylphenyl) acetamide

$^1\text{H-NMR}$ (CDCl_3 , δ - values): 7.53-7.46 (d, 2H, arom), 6.9-6.83 (d, 2H, arom.), 5.07 (t, 1H, vinylic proton), 3.79 (s, 3H- COH_3), 3.11-3.06 (t, 2H, N-CH_2)

IR (DCM) : 1657 cm^{-1} (amide carbonyl)

Example 58

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide (Compound No.58).

5 This compound was synthesized following the procedure as described in Example 56 using 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-(4-fluorophenyl) acetamide instead of 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-(4-methylphenyl) acetamide.

10 $^1\text{H-NMR}$ (CDCl_3) 7.58-7.53 (q, 4H, arom), 5.047 (d, 1H, vinylic proton), 3.13-3.078 (t, 2H, N- CH_2).

IR (DCM) : 1656 cm^{-1} (amide carbonyl)

Example 59

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No. 59).

15 This compound was synthesized following the procedure as described in Example 3 using methyl iodide and starting from methyl 2-hydroxy-2-cyclohexyl-2-phenyl acetate (J. Amer. Chem. Soc. 75, 2654 (1953)).

20 $^1\text{H-NMR}$ (CDCl_3) 7.42-7.20 (m, 10H, arom), 6.68 (b, 1H, NH), 3.56 (s, 2H, N- CH_2), 3.12-3.07 (m, 5H, - OCH_3 , piperazine protons, α -hydrogen), 2.41-2.38 (m, 2H, piperazine protons), 2.28 (m, 1H, α -H), 1.96-1.1 (m, 8H), 0.89 (m, 2H, cyclopropyl)

IR (DCM) : 1665 cm^{-1}

Example 60

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-ethyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.60).

25 This compound was synthesized following the procedure as described in Example 23, using 6-N-(3-azabicyclo[3.1.0]hexyl)-2-methoxy-2-cyclohexyl-2-phenyl acetamide instead of 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-phenyl acetamide in step a, and ethyl bromide instead of 3,5-difluoro benzyl bromide in step b of Example 23.

¹H-NMR (CDCl₃) 7.35-7.14 (m, 5H, arom.), 4.22 (m, 2H, N-CH₂), 3.57-3.43 (m, 5H, -OCH₃, piperazine protons, α -hydrogen), 2.47-2.38 (m, 2H, piperazine protons), 2.28 (m, 1H, α -H), 1.96-1.1 (m, 8H), 0.89 (m, 2H, cyclopropyl)

IR (DCM) : 1665cm⁻¹

5

Example 61

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-(2-propenyoxy)-2-phenyl acetamide (Compound No.61).

This compound was synthesized following the procedure as described in Example 3, using ethyl-2-hydroxy-2-cyclohexyl phenyl acetate instead of ethyl-2-hydroxy-2,2-diphenyl acetate in step (i) a, and ethyl-2-allyloxy-2-cyclohexyl-2-phenyl acetate instead of ethyl-2-allyloxy-2,2-diphenyl acetate in step (ii) a of Example 3.

¹H-NMR (CDCl₃): 7.48-7.20 (m, 10H, arom.), 6.0-5.12 (m, 3H, vinylic protons), 3.55 (s, 2H, N-CH₂), 3.12-3.09 (m, 2H, O-CH₂), 2.40-2.22 (m, 5H, piperazine protons, α -hydrogen) 1.7 TO 1.1 (m, 10H, cyclohexyl), 0.89 (m, 2H, cyclopropyl)

15 IR (DCM): 1678 cm⁻¹

Example 62

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.62).

This compound was synthesized following the procedure as described in Example 23 using 6-N-(3-azabicyclo[3.1.0]hexyl)-2-methoxy-2-cyclohexyl-2-phenyl acetamide instead of 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-phenyl acetamide in step a, and 4-methyl-3-pentenyl bromide instead of 3,5-difluoro benzyl bromide in step b of Example 23.

¹H-NMR (CDCl₃) 7.42-7.26(m, 5H, arom.), 4.08 (m, 1H, vinylic) 3.17 to 2.97 (m, 5H, -OCH₃, piperazine protons, α -hydrogen), 2.38-2.28 (m, 4H, piperazine protons N-CH₂), 2.09 (m, 1H, α -H), 1.96-1.1 (m, 18H, cyclohexyl, 2x-CH₃, -CH₂), 0.89 (m, 2H, cyclopropyl)

IR (DCM) : 1655cm⁻¹

Example 63

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2,4-difluorobenzyl))-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.63).

This compound was synthesized following the procedure as described in
 5 Example 23 using 6-N-(3-azabicyclo[3.1.0]hexyl)-2-methoxy-2-cyclohexyl-2-phenyl acetamide instead of 6-N-(3-azabicyclo[3.1.0]hexyl)-2-hydroxy-2-cyclohexyl-2-phenyl acetamide in step a, and 2,4-difluorobenzyl bromide instead of 3,5-difluoro benzyl bromide in step b of Example 23.

$^1\text{H-NMR}$: (CDCl_3) 8.19-8.01 (m, 3H, arom.), 7.36-6.86 (m, 5H , arom.),
 10 5.37 (s, 1H), 5.12-5.10 (s, 2H), 3.08 (s, 3H), 2.33-0.85 (m, 11H)

IR : 1670cm $^{-1}$

Example 64

Preparation of 1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 64).

15 **Step a:** Synthesis of 2-hydroxy-2-cyclopentyl-2-phenyl acetic acid. This was synthesized following the procedure in J. Amer. Chem. Soc. 75, 2654 (1953).

Step b: The amide was synthesized following the procedure in step c of Example 85 using 2-hydroxy-2-cyclopentyl-2-phenyl acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

20 Analytical data:

m.p. : 61-65°C

I.R. : 1658 cm $^{-1}$

$^1\text{H-NMR}$ (CDCl_3): 1.1-3 (due to cyclopentyl and bicyclic amine protons), 3.5 (s, 2H, N-CH₂) 6.43 (1H, OH, S), 7.22-7.58 (m, 10H, aromatic).

25

Example 65

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.65).

The compound was synthesized starting from Compound No. 64, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 41.

I.R. : 1658 cm⁻¹

5 ¹H-NMR (CDCl₃): 7.55-7.58 (m, 2H, aromatic) 7.22-7.35 (3H, m, aromatic) 6.35 (s, 1H, OH) 5.0 (t, 1H, allylic proton), 1.1-3.4 (Due to Aliphatic)

Example 66

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(3,4-methylenedioxyphenyl)ethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.66).

10

The compound was synthesized starting from Compound No. 64, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 29.

I.R. : 1665 cm⁻¹

15 ¹H-NMR (CDCl₃): 0.85-3.48 (due to aliphatic) 5.89 (s, 2H, methylenedioxy CH₂) 6.39 (s, 1H, OH), 6.39-7.58 (m, 8H, Aromatic)

Example 67

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.67).

20

The compound was synthesized starting from Compound No. 64, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 27. Yield 98%

IR (DCM) cm⁻¹ 1650 (amide carbonyl)

25 ¹H-NMR (CDCl₃, δ - values) 7.59-7.13(m, 10H, aromatic), 3.16-3.13 (m, 2H, N-CH₂), 3(m, 1H, α -H in cyclopentyl), 2.68-2.59(m, 3H, piperazine and α -H), 2.37-2.34(m, 2H, piperazine), 1.62-1.1(m, 10H, cyclopentyl and benzylic CH₂), 0.88(m, 2H, cyclopropyl).

Example 68

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(2,3-dihydrobenzofuran-5-yl)ethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.68).

5 The compound was synthesized starting from Compound No. 64 which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 28.

IR (DCM) cm^{-1} 1659 (amide carbonyl)

10 $^1\text{H-NMR}$ (CDCl_3) 7.59-6.64(m, 10H, aromatic), 4.54-4.49(t,2H, O- CH_2), 3.17-3.12(m, 5H, piperazine, N- CH_2 and α -Hydrogen), 2.85-2.84(m, 1H, α -H in cyclopentyl), 2.59-2.54(m, 4H, piperazine and benzofuran CH_2), 2.36-2.33(m, 2H, benzylic CH_2), 1.67-1.1(m, 8H, cyclopentyl), 0.87(m, 2H, cyclopropyl).

Example 69

15 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-methyl-pyrid-6-yl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.69).**

Step a: Synthesis of 2-chloromethyl-5-methyl pyridine hydrochloride: To 2-hydroxymethyl-5-methyl pyridine (123mg, 1mmol) in chloroform at 0°C , thionyl chloride (2.5mmol) was slowly added. The reaction mixture was then stirred at 0°C overnight. The volatile material was removed under reduced pressure and the residue was crystallized using hexane.

Step b: The title compound was synthesized following the procedure as described in Example 27, using 2-chloromethyl-5-methyl pyridine hydrochloride instead of 2-phenyl ethyl bromide.

IR (DCM) cm^{-1} 1660 (amide carbonyl)

25 $^1\text{H-NMR}$ (CDCl_3) 7.59-6.95(m, 8H, aromatic), 3.67(s, 2H, pyridyl CH_2), 3.13-2.98 (m, 4H, piperazine, α -H in cyclopentyl and α -hydrogen), 2.5(s, 3H, methyl), 2.46-2.43(m, 2H, piperazine), 1.7-1.23(m, 8H, cyclopentyl), 0.88(m, 2H, cyclopropyl).

Example 70

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-(2,3-dihydro benzofuran-5-yl) acetyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.70).

5 The compound was synthesized starting from Compound No. 64, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 30.

IR (DCM) cm^{-1} 1716 (keto), 1663 (amide carbonyl)

10 $^1\text{H-NMR}$ (CDCl_3) 7. 9-6.74(m, 8H, aromatic), 4.66-4.6(t,2H, O- CH_2), 3.71(s, 2H, N- CH_2), 3.24-3.14 (m, 5H, piperazine, benzofuran- CH_2 and α -Hydrogen), 3(m, 1H, α -H in cyclopentyl), 2.58-2.55(m, 2H, piperazine), 1.67-1.25(m, 8H, cyclopentyl), 0.88(m, 2H, cyclopropyl).

Example 71

15 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(benzofuran-5-yl)ethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.71).**

The compound was synthesized starting from Compound No. 64, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 31.

IR (DCM) cm^{-1} 1658 (amide carbonyl)

20 $^1\text{H-NMR}$ (CDCl_3) 7.58-6.68(m, 10H, aromatic), 3.17-3.15(m, 2H, N- CH_2), 3 (m, 1H, α -H in cyclopentyl), 2.86-2.85(m, 1H, α -Hydrogen), 2.76-2.74(m, 2H, piperazine), 2.64-2.62(m, 2H, piperazine), 2.38-2.34(m,2H, benzylic CH_2), 1.53-1.23(m, 8H, cyclopentyl), 0.87-0.85 (m, 2H, cyclopropyl).

Example 72

25 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cycloheptyl-2-hydroxy-2-phenyl acetamide (Compound No.72).**

Step a: Synthesis of 2-hydroxy-2-cycloheptyl-2-phenyl acetic acid. This was synthesized following the procedure in J. Amer. Chem. Soc. 75, 2654 (1953).

Step b: The title compound was synthesized following the procedure as described in step c of Example 85 using 2-hydroxy-2-cycloheptyl-2-phenyl acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

IR (DCM) 1659 cm⁻¹ (amide carbonyl)

5 ¹H-NMR (CDCl₃) 7.57-7.0(m, 10H, aromatic), 3.52(s, 2H, N-CH₂), 3.07 –2.91 (m, 3H, α -H in cyclopentyl , piperazine protons), 2.60(m, 1H, α -Hydrogen in cyclo heptyl), 2.37-2.32(m, 2H, piperazine), 1.7-0.87(m, 14H, cycloheptyl, cyclopropyl protons).

Example 73

10 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cycloheptyl-2-hydroxy-2-phenyl acetamide (Compound No.73).**

The compound was synthesized starting from Compound No. 72, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in example 41.

15 IR (DCM) cm⁻¹ 1659.8 (amide carbonyl), 3397.7 (O-H)

¹H-NMR (CDCl₃) 7.69-7.26(m, 5H, aromatic), 6.38(m,1H, vinylic), 3.17-3.15(m, 2H, N-CH₂), 2.86-2.63 (m, 4H, piperazine, α -H in cycloheptyl, α -Hydrogen), 2.38(m, 2H, piperazine), 1.41-1.11(m, 12H, cycloheptyl), 0.87-0.85 (m, 2H, cyclopropyl).

Example 74

20 **Preparation of 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.74).**

Step a : Preparation of 2-amino-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamide: 2-(Boc-amino)propionic acid was condensed with (1 α ,5 α ,6 α)-6-amino-3-azabicyclo[3.1,0]hexane, following the procedure as described in step c of Example 85. . The N-Boc compound thus obtained was deprotected with 10%

25 trifluoro acetic acid in dichloromethane to afford the free amino compound.

Step b : Compound No. 74 was prepared through the reaction of the compound obtained in step a above with 2-hydroxy-2-cyclohexyl-2-phenyl acetic acid, following the procedure given in step c of Example 85.

¹H-NMR(CDCl₃) : 7.6 – 7.15 (m, 10H, arom.), 4.22 (m, 1H), 3.55 (d, 2H), 3.08 (q, 2H), 2.95 (q, 2H), 2.86 (s, 1H), 2.37 (m, 2H), 2.35 (m, 1H), 1.65 (d, 1H), 1.25 (m, 9H), 0.88 (q, 2H).

Example 75

5 **Preparation of 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)acetamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.75).**

This compound was synthesized following the procedure as described in Example 74 using 2-(Boc-amino)acetic acid in step a instead of 2-(Boc-amino)propionic acid.

10 ¹H-NMR(CDCl₃) 7.61-7.18 (m, 10H, arom), 3.78-3.76 (d, 2H, α -methylene), 3.54 (s, 2H, benzylic protons).

IR: 1666 cm⁻¹ (broad, amide carbonyl)

Example 76

15 **Preparation of 3-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)propionamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.76).**

This compound was synthesized following the procedure as described in Example 74, using 3-(Boc-amino)propionic acid in step a instead of 2-(Boc-amino)propionic acid.

20 ¹H-NMR(CDCl₃) 7.59-7.2 (m, 10H, arom), 3.56 (s, 2H, benzylic protons), 3.46-3.44 (d, 2H, N-CH₂), 3.08-3.05 (d, 2H, piperazine protons).

IR : 1651 cm⁻¹ (amide carbonyl).

Example 77

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-3-cyclohexyl-3-hydroxy-3-phenyl propionamide (Compound No.77).

25 **Step a:** Preparation of 3-hydroxy-3-phenyl-3-cyclohexyl propionic acid.

This compound was synthesized following the procedure given in J.Chem. Soc.(C), 2799 (1969).

Step b: The title compound was synthesized following the method as given in Example 85, step c using 3-hydroxy-3-phenyl-3-cyclohexyl propionic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

¹H-NMR (CDCl₃) ; 7.37-7.16 (m, 10H, arom.); 5.7 (s, broad, NH), 5.0 (s, 1H, -OH),

5 3.48 (s, 2H, benzylic protons), 2.96-2.93 (m, 2H, piperazine protons), 2.73(m, 2H, piperazine protons), 2.52-2.48 (m, 2H, -CH₂-, α to carbonyl).

IR (DCM) : 1625 cm⁻¹ (amide carbonyl).

Example 78

10 **Preparation of 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)acetamido)-3-cyclohexyl-3-hydroxy-3-phenyl propionamide (Compound No.78).**

This compound was synthesized following the procedure as described in Example 75, but using 3-hydroxy-3-phenyl-3-cyclohexyl-propionic acid in step b instead of 2-hydroxy-2-cyclohexyl-2-phenyl acetic acid.

¹H-NMR(CDCl₃) 7.36-7.17 (m, 10H, arom.), δ 3.66-3.5 (m, 4H, benzylic protons, N-

15 CH₂-CO)

IR : 1654 cm⁻¹ (broad amide carbonyl)

Example 79

20 **Preparation of 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)propionamido)-2-cyclohexyl-3-hydroxy-3-phenyl propionamide (Compound No.79).**

This compound was synthesized following the procedure as described in Example 74, but using 3-hydroxy-3-phenyl-3-cyclohexyl-propionic acid in step b instead of 2-hydroxy-2-cyclohexyl-2-phenyl acetic acid.

¹H-NMR(CDCl₃) 7.5-7.15 (m, 10H, arom.), δ 4.15 (m, 1H, CH), δ 3.57 (s, 2H,

25 benzylic)

IR : 1664 cm⁻¹ (broad, amide carbonyl)

Example 80

Preparation of (1 α ,5 α ,6 α)-2-[6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-N-propionamido-2-cyclohexyl-2-hydroxy-2-phenyl acetate. (Compound No.80).

Step a : Preparation of 1-chloro-(1 α ,5 α ,6 α)-2-[6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-N-propionamide: Equimolar quantities of 2-chloropropionyl chloride and (1 α ,5 α ,6 α)-3-N-benzyl-6-amino-3-azabicyclo[3.1.0]hexane were reacted in dichloromethane in the presence of triethylamine. The reaction mixture was worked up by the addition of water and the compound was isolated from the organic phase.

Step b : Compound No. 80 was prepared by the reaction of the compound obtained in step – a with 2-hydroxy-2-cyclohexyl-2-phenyl acetic acid, following the procedure given in step b of Example 10.

$^1\text{H-NMR}$ (CDCl_3) ; 7. 7-7.2 (m, 10H, arom.); 5.19 (m, 1H, ester -CH), 3.5 (s, 2H, benzylic protons), 2.95(m, 3H, piperazine protons, α -H), 2.27(q, 2H, piperazine protons), 1.68 (m, 5H), 1.5 (d, 3H, α - CH_3), 1.2 (m, 7H)

IR (DCM) : 1669 cm^{-1} (amide carbonyl), 1733 cm^{-1} (ester carbonyl)

Example 81

Preparation of (2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.81).

Step a: Preparation of (2R)-2-hydroxy-2-cyclopentyl-2-phenyl acetic acid : Synthesized as per reported procedure of Paul T. Grover, et.al. J. Org. Chem. 2000, 65, 6283 – 6287.

Step b: The amide was synthesized following the procedure as described in step c of Example 85 using (2R)-2-hydroxy-2-cyclopentyl-2-phenyl acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

Step c: The title compound was synthesized starting from the compound obtained in step b, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 41.

$^1\text{H-NMR}(\text{CDCl}_3)$ 7.58 – 7.23 (m,5H, aromatic), 6.34 (s, 1H), 5.05 (m, 1H, vinylic) 3.11 to 3.08 (m, 2H, N- CH_2) 2.98 (m , 1H, α -hydrogen), 2.96 (s, 1H), 2.35 to 2.3 (

m, 4H, piperazine protons) 2.09 to 1.17 (m, 16H, aliphatic , 2x CH₃, cyclopentyl), 0.88 (m, 2H, cyclopropyl)

I.R.(DCM) : 1652cm⁻¹

Example 82

5 Preparation of (2R) - (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,4-methylenedioxyphenyl)ethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.82).

Step a: Preparation of (2R)-2-hydroxy-2-cyclopentyl-2-phenyl acetic acid :
Synthesized as per reported procedure of Paul T. Grover, et.al. J. Org. Chem. 10 2000, 65, 6283 – 6287.

Step b: The amide was synthesized following the procedure as described in step c of Example 85 using (2R)-2-hydroxy-2-cyclopentyl-2-phenyl acetic acid instead of 2-hydroxy-2,2-diphenyl acetic acid.

Step c: The title compound was synthesized starting from the compound as synthesized in step b, which was debenzylated following the method as described in step a of Example 23, and then N-alkylated as given in Example 29.

¹H-NMR(CDCl₃) 7.59-6.54 (m, 8H, arom.), 5.9 (s, 2H, methylenedioxy) 3.18 (t, 2H, N-CH₂- C), 3.0 (m, 1H), 2.68 (s, 1H), 2.5 (m, 3H, piperazine, α -hydrogen), 2.38 -2.34 (m, 2H, piperazine).2.17 (m, 12 H, aliphatic)

20 IR (DCM) : 1653 cm⁻¹ (amide carbonyl)

Example 83

Preparation of (2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide succinate salt. (Compound No.83).

25 (2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No 81, 1 mmol) was dissolved in ethanol (10 ml) and a solution of succinic acid (1mmol) in ethanol (5 ml) was added and stirred at 60°C for 1 hr . The reaction mixture was then concentrated by the evaporation of solvents under reduced pressure and the resulting solid was 30 triturated from diethyl ether to afford the title compound.

m.p. 148 – 150 °C, $[\alpha]_D^{25\text{OC}} = + 17.77^\circ$

CHN analysis : C = 66.77 (67.176), H = 8.09 (8.05), N = 6.02 (5.59).

Example 84

Preparation of (2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-3-(4-methyl-3-pentenyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide L-(+)-tartarate salt. (Compound No.84).

(2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-3-(4-methyl-3-pentenyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 81, 1 mmol) was dissolved in ethanol (10 ml) and a solution of L-(+) -tartaric acid (1mmol) in ethanol (5 ml) was added and stirred at 60°C for 1 hr. The reaction mixture was then concentrated by the evaporation of solvents under reduced pressure and the resulting solid was triturated from diethyl ether to afford the title compound.

m.p. 49°C.

Example 85

15 Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-phenylacetamide (Compound No.85)

Step a: Synthesis of 2-hydroxy-2-cyclohexyl-2-phenylacetic acid.

The title compound was prepared following the procedure as described in J. Amer. Chem. Soc., 75, 2654 (1953).

20 Step b: Synthesis of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-phenylacetamide

To a solution of (1 α ,5 α ,6 α)-3N-benzyl-6-amino3-azabicyclo-[3.1.0]hexane, as per reported procedure of Braish, T.F. et al. Syn Lett. 1100(1996). (1 mmol, 0.188 gm) in DMF (5 ml) was added 2-hydroxy-2,2-diphenyl acetic acid (1 mmol, 0.225 gm) and cooled to 0°C. The reaction mixture was treated with hydroxy benzotriazole (1 mmol, 0.135g) followed by N-methyl morpholine (2 mmol, 0.202 gm) and stirred at 0°C for 0.5 hours. Then was added EDC (1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride, (1 mmol, 0.192 gms).

The reaction mixture after stirring at 0°C for 1 hr. was later stirred at room temperature overnight. Then the RM was poured into cold water and extracted with ethyl acetate. The combined organic layer were washed with water and dried over sodium sulphate. The crude compound obtained after removing the solvent was 5 purified by column chromatography (silicagel 100-200 mesh), eluting the compound with 30-70 ethylacetate-hexane mixture.

Step c: Synthesis of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-phenylacetamide

To a solution of the compound of step b (0.3 g, 0.74 mmol) in methanol (10.0 ml), 10 10% Pd-C (0.3g) was added and the reaction mixture was stirred at room temperatrue for 2 hours under an atmosphere of H₂. The reaction mixture was filtered through a bed of hyflo and the bed was washed with methanol (10.0 ml). The filtrate was concentrated under vacuum to give the title compound in 77% (0.18 g, 0.57 mmol) yield.

15 ¹HNMR (CDCl₃): δ 7.60 (d, J=6 Hz, 2H), 7.24-7.37 (m, 3H), 6.63 (brd, 1H), 3.07-3.15 (m, 2H), 2.34-2.44 (m, 3H), 1.19-1.39 (m, 10H), 1.02 (d, J=6Hz, 2H), 0.90 (m, 1H)

IR (KBr) : 1665.6cm⁻¹

Example 86

20 **Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-Fluorophenyl)acetamide (Compound No.86)**

Step a: Synthesis of 2-(4-fluorophenyl)-2-cyclohexyl-2-hydroxy acetic acid.

The compound was synthesized as per reported procedure in Syn. Comm., 11 (12), 943-946 (1981).

25 **Step b:** Synthesis of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide

This was synthesized in direct analogy to the procedure of step b of Example 85, using the product of step a here instead of that of Example 85.

Step c: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-phenylacetamide

This compound was prepared in 90% yield following a procedure directly analogous to that of step c, Example 85.

5 IR (KBr): 1663.9 cm⁻¹

Example 87

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl)acetamide (Compound No.87)

Step a: Synthesis of 2-(4-methoxyphenyl)-2-cyclohexyl-2-hydroxy acetic acid

10 This compound was synthesized as per reported procedure in Syn. Comm. 11 (12), 943-946 (1981).

Step b: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide

This was synthesized in direct analogy to the procedure of step b of Example 85, 15 using the product of step a here instead of that of Example 85.

Step c: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl)acetamide

This compound was prepared in 90% yield by following a procedure directly analogous to that of step c, Example 85.

20 ¹H NMR (CDCl₃): δ 7.52-7.58 (m, 2H), 6.82-6.90 (m, 3H), 3.72 (s, 3H), 3.16-3.32 (m, 1H), 2.60-2.84 (m, 2H), 2.06-2.38 (m, 2H), 1.57-1.77 (m, 5H), 1.17-1.37 (m, 7H), 0.92-0.96 (m, 1H)

IR (KBr): 1659.3 cm⁻¹

Example 88

25 **Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl)acetamide (Compound No.88)**

Step a: Synthesis of 2-(4-methylphenyl)-2-cyclohexyl-2-hydroxy acetic acid.

This compound was synthesized as per reported procedure in Syn. Comm., 11 (12), 943-946 (1981)

Step b: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl)acetamide

5 This was synthesized in direct analogy to the procedure of step b of Example 85, using the product of step a here, instead of that of Example 85.

Step c: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl)acetamide

10 This compound was prepared in 90% yield by following a procedure directly analogous to that of step c, Example 85.

^1H NMR (CDCl_3): δ 7.46 (d, $J=6\text{Hz}$, 2H), 7.11-7.18 (m, 2H), 6.96 (brs, 1H), 3.02-3.07 (m, 2H), 2.50-2.80 (m, 1H), 2.31-2.35 (m, 5H), 1.58-1.67 (m, 5H), 1.10-1.35 (m, 7H), 0.80-0.90 (m, 1H)

IR (KBr) : 1660.6 cm^{-1}

15 **Example 89**

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (Compound No.89)

Step a: Synthesis of 2-hydroxy-2-cyclopentyl-2-phenyl acetic acid.

This was synthesized following the procedure in J. Amer. Chem. Soc., 75, 2654 (1953)

Step b: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide

This was synthesized in direct analogy to the procedure of step b of Example 85, using the product of step a here instead of that of Example 85.

25 **Step c:** Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide

This compound is prepared in 90% yield following a procedure directly analogous to that of step c of Example 85.

¹H NMR (CDCl₃): δ 7.57 (d, J=6Hz, 2H), 7.15-7.35 (m, 3H), 6.52 (brs, 1H), 2.99-3.13 (m, 3H, including -OH), 2.84-2.99 (m, 1H), 2.35-2.38 (m, 2H), 1.25-1.67 (m, 10H),

5 1.15-1.20 (m, 1H)

IR (DCM) : 1650.9 cm⁻¹

Example 90

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cycloheptyl-2-hydroxy-2-phenylacetamide (Compound No.90)

10 **Step a:** Synthesis of 2-hydroxy-2-cycloheptyl-2-phenyl acetic acid.

This was synthesized following the procedure in J. Amer. Chem. Soc., 75, 2654 (1953).

Step b: Synthesis of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2-cycloheptyl-2-phenylacetamide

15 This was in direct analogy to the procedure of step b of Example 85, using the product of step a here instead of that of Example 85.

Step c: Synthesis of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cycloheptyl-2-hydroxy-2-phenylacetamide

20 This compound is prepared in 90% yield following a procedure directly analogous to that of step c of Example 85.

Example 91

Preparation of (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclobutyl-2-hydroxy-2-phenylacetamide (Compound No.91)

Step a: Synthesis of 2-hydroxy-2-cyclobutyl-2-phenyl acetic acid.

25 This was synthesized following the procedure in J. Amer. Chem. Soc., 75, 2654 (1953).

Step b: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclobutyl-2-hydroxy-2-phenylacetamide

This was synthesized in direct analogy to the procedure of step b of Example 85, using the product of step a here instead of that of Example 85.

5 **Step c:** Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclobutyl-2-hydroxy-2-phenylacetamide

This compound is prepared in 90% yield following a procedure directly analogous to that of step c of Example 85, using the product of step a here instead of that of Example 85.

10 m.p. : 150°C

^1H NMR (CDCl_3): δ 7.46-7.49 (m, 2H), 7.29-7.36 (m, 3H), 6.31 (brs, 1H), 5.14-3.40 (m, 1H), 3.05-3.14 (m, 2H), 2.86-2.90 (m, 2H), 2.39 (s, 1H), 1.75-2.05 (m, 6H), 1.25-1.51 (m, 2H)

IR (KBr) : 1669.4 cm^{-1}

15

Example 92

Preparation of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl)-2-cyclopropyl-2-hydroxy-2-phenylacetamide (Compound No.92)

Step a: Synthesis of 2-hydroxy-2-cyclopropyl-2-phenyl acetic acid.

This was synthesized following the procedure in J. Amer. Chem. Soc., 75, 2654 (1953).

Step b: Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclopropyl-2-hydroxy-2-phenylacetamide

This was synthesized in direct analogy to the procedure of step b of Example 85, using the product of step a here instead of that of Example 85.

25 **Step c:** Synthesis of ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclopropyl-2-hydroxy-2-phenylacetamide.

This compound is prepared in 96% of yield following a procedure directly analogous to that of step c, of Example 85.

¹HNMR (CDCl₃ + DMSO-d₆): δ 7.56-7.63 (m, 2H), 7.28-7.35 (m, 3H), 5.25 (brs, 1H),

3.03-3.14 (m, 2H), 2.85-2.90 (m, 3H), 1.66-1.75 (m, 1H), 1.55-1.56 (m, 2H), 0.38-

5 0.56 (m, 4H)

IR (KBr) : 1667.1 cm⁻¹

Example 93

Preparation of (1 α ,5 α ,6 α)-1-[6-N-(3-azabicyclo[3.1.0]hexyl)]-N-acetamido-2-hydroxy-2-cyclohexyl-2-phenylacetate (Compound No.93)

10 Step a: Preparation of 2-hydroxy-2-cyclohexyl phenyl acetic acid

This was prepared following the procedure as described in J. Amer. Chem. Soc., 75, 2654 (1953).

Step b: Preparation of (1 α ,5 α ,6 α)-6N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-chloro acetamide

15 To a solution of the corresponding amine synthesized following the procedure of T.F. Braish et. al., Synlett., 1996, 1100 (0.6g, 3.2 mmol) in dichloromethane (15 ml) at -20°C, triethylamine (1.34 ml) and chloroacetyl chloride were added dropwise. The reaction mixture was stirred for 2 hrs. at -20°C. The reaction mixture was cooled to room temperature, diluted with dichloromethane (15 ml) and washed with water. The
20 organic layer was dried over anhydrous sodium sulphate and concentrated. The residue obtained was purified by column chromatography using 40% ethylacetate-hexane as the eluent mixture to get 63.1% of the title compound.

Step c: Preparation of (1 α ,5 α ,6 α)-1-[6N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)]-N-acetamido-2-cyclohexyl-2-hydroxy-2-phenylacetate

25 To a solution of compound of step a (0.304 g, 1.3 mmol) and the compound of step b (0.23g, 0.87 mmol) in xylene (15 ml) was added 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (0.2 g, 1.3 mmol) and the reaction mixture was refluxed for 3 hours. The reaction mixture was directly adsorbed over silicagel and purified by column

chromatography using 60% ethylacetate in hexane to get the title compound in 95% yield.

Step d: of $(1\alpha,5\alpha,6\alpha)$ -1-[6-N-(3-azabicyclo-[3.1.0]hexyl)]-N-acetamido-2-hydroxy-2-cyclohexyl-2-phenylacetate.

5 To a solution of the corresponding N-benzyl derivative (0.245g, 0.53 mmol) in methanol (20.0 ml) 10% Pd-C (0.1 g, 50% wet) was added and the reaction mixture was hydrogenated at 60 PSI for 3.50 hours at room temperature. The reaction mixture was filtered through a bed of hyflo and the bed was washed with methanol. The filtrate was concentrated under vacuum to get the title compound in 91%.
 10 (0.18g, 0.48 mmol) yield.

^1H NMR (CDCl_3): δ 7.72 (d, $J=6\text{Hz}$, 2H), 7.35-7.56 (m, 3H) 4.94 (d, $J=15\text{Hz}$, 1H), 4.47 (d, $J=15\text{ Hz}$, 1H), 5.04-3.70 (m, 2H), 2.50 (s, 1H), 2.36-2.41 (m, 2H), 1.89-1.93 (m, 1H), 1.70-1.80 (m, 2H), 1.19-1.38 (m, 10H)

IR (DCM): 1738.4, 1666.5 cm^{-1}

15 **Example 94**

Preparation of $(1\alpha,5\alpha,6\alpha)$ -1-[6-N-(3-azabicyclo-[3.1.0]hexyl)]-N-propionamido-2-hydroxy-2-cyclohexyl-2-phenylacetate (Compound No. 94)

This compound was synthesized in direct analogy to the procedure of Example 93 by using 2-chloropropionyl chloride in step b, Example 93 instead of chloroacetyl
 20 chloride.

^1H NMR (CDCl_3): δ 7.62-7.72 (m, 2H), 7.29-7.50 (m, 3H), 5.19-5.28 (s, 1H), 3.04-3.11 (m, 2H), 2.26-2.38 (m, 2H), 1.86-1.90 (m, 2H), 1.16-1.55 (m, 15H)

IR (KBr) : 1735.2, 1663.9 cm^{-1}

Example 95

25 **Preparation of $(1\alpha,5\alpha,6\alpha)$ -4-[6-N-(3-azabicyclo[3.1.0]hexyl)]-N-(tert-butyloxy carbonyl)butyl-1-[2-hydroxy-2,2-bis-(4-fluorophenyl)]acetate (Compound No. 95)**

Step a: Preparation of 2-hydroxy-2,2-bis-(4-fluorophenyl) acetic acid.

(i) Preparation of 1,2-Bis (4-fluorophenyl)-2-hydroxy-ethanone

To a solution of commercially available 4-fluorobenzaldehyde (24.8 g, 200 mmol) in ethanol (30 ml) and sodium cyanide (2.13g, 43.5 mmol) in water (20 ml) was added and the resulting solution was refluxed for 1 hour. The reaction mixture was cooled to 0°C and diluted with water. The solid so separated was filtered and washed with cold water thoroughly and used as such in the next step.

5 (ii) Preparation of 1,2-Bis (4-fluorophenyl)-2-oxo-ethanone

To the compound obtained in the above step was added conc. nitric acid (40 ml) and the resulting solution was refluxed for 4 hours. The solution 10 was cooled and poured onto chilled water (500 ml) under stirring and the solid so produced was filtered, washed with water and dried to give the title compound in 63% yield.

10 (iii) Preparation of 2-hydroxy-2,2-bis-(4-fluorophenyl)acetic acid.

To a solution of KOH (21.0 gm) in water (42.0 ml), ethanol (54.0 ml) 15 followed by the compound obtained from the above step (25.0g, 101mmol) was added and the resulting solution was refluxed for 30 minutes and poured into a glass plate and left overnight at room temperature. The semisolid obtained was dissolved in water (400 ml) and washed with ethyl acetate. The pH of the aqueous layer was adjusted to acidic with 50% HCl, extracted with ethyl acetate. The ethyl acetate layer was dried over 20 anhydrous Na₂SO₄ and concentrated to give the title compound in 45% yield (12.0 g, 45 mmol).

Step b: Preparation of 6-(N- α -bromobutyl, N-tert-butyloxy carbonyl, N-3-benzyl-3-azabicyclo [3.1.0]hexane).

25 A solution of 6-N-tert-butyloxy carbonyl, N-3-benzyl-3-azabicyclo[3.1.0]hexane (1mmol) in DMF (5 ml) was added to a cold suspension of sodium hydride in DMF under nitrogen. The reaction mixture stirred at room temperature for 1 hr, cooled to 0°C and it was added to a solution of 1,4-dibromo butane (2 mmol) in DMF. The reaction mixture was stirred at room temperature for 3 hours, and then quenched by

addition of aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over sodium sulphate. The crude compound obtained was purified by column chromatography, eluting the compound with 25:75, ethylacetate-hexane mixture.

5 **Step c:** Preparation of ($1\alpha,5\alpha,6\alpha$)-4-[6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)]-N-(tert-butyloxycarbonyl)butyl-1-[2-hydroxy-2,2-bis-(4-fluorophenyl)]acetate

To a solution of the above prepared bromoderivative (0.25g, 0.59 mmol) in toluene (20.0 ml), 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (0.135 ml, 0.89mmol) followed by the hydroxy acid of step a (0.312g, 1.18 mmol) was added. The reaction

10 mixture was refluxed for 14 hours cooled and adsorbed directly onto silica gel and purified by column chromatography using 15% ethyl acetate in hexane to give the title compound in 100% (0.36g. 0.59 mmol) yield.

Step d: ($1\alpha,5\alpha,6\alpha$)-4-[6-N-(3-azabicyclo-[3.1.0]hexyl)]-N-tert-butyloxy carbonyl) butyl-1-[2-hydroxy-2,2-bis-(4-fluorophenyl)]acetate

15 To a solution of the corresponding N-benzyl derivative (0.4 g, 0.66 mmol) in methanol (20.0 ml), 10% Pd-C (0.2 g, 50% wet) was added and the resulting solution was hydrogenated at 50 p.s.i. and at room temperature for 2 hr. The reaction mixture was filtered through a bed of hyflo and the bed was washed with methanol (20.0 ml). The filtrate was concentrated to give the title compound as oil in 82%

20 (0.28g, 0.54 mmol) yield.

¹HNMR (CDCl₃): δ 7.38-7.43 (m, 4H), 7.01-7.07 (m, 4H), 4.27-4.31 (m, 2H), 2.93-3.19 (m, 5H), 2.43-2.46 (m, 1H), 1.28-1.63 (m, 13H).

IR (DCM) : 1731, 1685 cm⁻¹

Example 96

25 **Preparation of ($1\alpha,5\alpha,6\alpha$)-4-[6-N-(3-azabicyclo-[3.1.0]hexyl)]-N-(tert-butyloxycarbonyl)butyl-1-[2-propyloxy-2,2-bis-(4-fluorophenyl)]acetate (Compound No. 96)**

Step a: Preparation of 2-propyloxy-2,2-bis-(4-fluorophenyl)acetic acid

(i) Preparation of 2-hydroxy-2,2-bis-(4-fluorophenyl) acetic acid.

This was synthesized as described in step a, of Example 85.

(ii) Preparation of 2-hydroxy acetic acid 2,2-bis-(4-fluorophenyl) ethyl ester

To a solution of the compound of the above step (50g, 18.9 mmol) in ethanol (100.0 ml) at 0°C thionyl chloride (5.0 ml) was added and the resulting solution was refluxed for 4 hr. Ethanol was concentrated under vacuum and the residue was purified by column chromatography using 20% ethyl acetate in hexane to give the title compound as liquid in 91% (5.08, 17.2 mmol) yield.

(iii) Preparation of 2,2-bis-(4-fluorophenyl)-2-propoxy acetic acid ethyl ester

To a solution of sodium hydride (0.72 g, 15.42 mmol) in DMF (1.0 ml) at 0°C, the hydroxy ester (1.5 g, 5.14 mmol) in DMF (5.0 ml) was added and stirred at ROOM TEMPERATURE for 30 minutes. The reaction mixture was cold to 0°C and bromo propane (0.95 g, 7.7 mmol) was added and stirred for 4 hr. at ROOM TEMPERATURE. It was diluted with water, extracted with ethyl acetate, dried and concentrated. The residue was purified by column chromatography using 10% ethyl acetate in hexane to get the title compound as a liquid in 46% (0.79g, 2.36 mmol) yield.

(iv) Preparation of 2-propyloxy-2,2-bis-(4-fluorophenyl) acetic acid

To a solution of the ester (0.7g, 2 mmol) in methanol (20.0 ml), 1N LiOH (2.0 ml) was added and the reaction mixture was stirred at ROOM TEMPERATURE for 12 hr. Methanol was concentrated under vacuum, the residue was taken in water (50.0 ml) and washed with ethyl acetate. The aqueous layer was neutralized with acetic acid and extracted with ethyl acetate, dried and concentrated under vacuum to give the title compound as an oil in 47% (0.3 g, 0.94 mmol) yield.

¹HNMR (CDCl₃): δ 7.44-7.49 (m, 4H), 7.04-7.09 (m, 4H), 4.21-4.23 (m, 2H), 3.20-3.34 (m, 4H), 3.05-3.11 (m, 2H), 2.33-2.72 (m, 3H), 1.32-1.69 (m, 17H), 0.97 (t, J=6Hz, 3H),

IR (DCM) : 1742.2, 1693.8 cm⁻¹

Step b: Preparation of 6-(N- α -bromobutyl, N-tert-butyloxy carbonyl, N-3-benzyl-3-azabicyclo [3.1.0] hexane)

Prepared as described in step b of Example 85.

5 **Step c:** Preparation of (1 α ,5 α ,6 α)-4-[6-N-(3-azabicyclo-[3.1.0]hexyl-3-benzyl)]-(tert-butyloxy carbonyl) butyl-1-[2-propyloxy-2,2-bis-(4-fluorophenyl)]acetate

This was synthesized following the procedure of step c of Example 85 in 58% yield.

10 **Step d:** Preparation of (1 α ,5 α ,6 α)-4-[6-N-(3-azabicyclo-[3.1.0]hexyl)]-N-tert-butyl-1-[2-propyloxy-2,2-bis-(4-fluorophenyl)] acetate

The title compound was prepared following the procedure of step d, Example 85 in 64% yield.

15 1HNMR (CDCl₃): δ 7.44-7.49 (m, 4H), 7.04-7.09 (m, 4H), 4.21-4.23 (m, 2H), 3.20-3.34 (m, 4H), 3.05-3.11 (m, 2H), 2.33-2.72 (m, 3H), 1.32-1.69 (m, 17H), 0.97 (t, J=6Hz, 3H)

IR (DCM) : 1742.2, 1693.8 cm⁻¹

Example 97

Preparation of (1 α ,5 α ,6 α)-6N-(3-azabicyclo-[3.1.0]hexyl)-2,2-diphenyl acetamide (Compound No.97)

20 **Step a:** Preparation of 2,2-diphenyl acetic acid

Available commercially from Lancaster Synthesis (Windham, NH).

Step b: Preparation of (1 α ,5 α ,6 α)-3N-benzyl-6-amino-3-azabicyclo-[3.1.0]hexane

Synthesized as per reported procedure of Braish, T.F. et. al., Synlett., 1100 (1996).

Step c: Preparation of ($1\alpha,5\alpha,6\alpha$)- $6N$ -(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2,2-diphenyl acetamide

This was prepared by following the procedure of step b of Example 85` in 85% yield.

5 **Step d:** Preparation of ($1\alpha,5\alpha,6\alpha$)- $6N$ -(3-azabicyclo-[3.1.0]hexyl)-2,2-diphenyl acetamide

This was synthesized from the corresponding N-benzyl derivative in 72% yield by following the procedure of step c, Example 85.

10 1H NMR ($CDCl_3$): δ 7.24-7.30 (m, 10H), 5.62 (brs, 1H), 4.83 (s, 1H), 3.01-3.08 (m, 2H), 2.24-2.34 (m, 3H), 1.39-1.45 (m, 2H).

IR (DCM) : 1650.6 cm^{-1}

Example 98

Preparation of ($1\alpha,5\alpha,6\alpha$)- $6N$ -(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.98)

15 **Step a:** Preparation of 2-cyclohexyl-2-phenyl-2-methoxy acetic acid

This was prepared according to the procedure described in J. Amer. Chem. Soc., 75, 2654, 1953.

Step b: Preparation of ($1\alpha,5\alpha,6\alpha$)- $3N$ -benzyl-6-amino-3-azabicyclo-[3.1.0]hexane

Synthesized as per reported procedure of Braish, T.F. et. al., Synlett, 1100 (1996).

Step c: Preparation of ($1\alpha,5\alpha,6\alpha$)- $6N$ -(3-azabicyclo-[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide

This was prepared in 40% yield by following the procedure of step b, Example 85.

25 **Step d:** Preparation of ($1\alpha,5\alpha,6\alpha$)- $6N$ -(3-azabicyclo-[3.1.0]hexyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide

This was synthesized from the corresponding N-benzyl derivative by following the procedure of step c, Example 85 in 64% yield.

1H NMR (CDCl_3): δ 7.27-7.41 (m, 5H), 6.76 (brs, 1H), 3.21 (d, $J=12\text{Hz}$, 2H), 3.09 (s, 3H), 2.97 (d, $J=12\text{Hz}$, 2H), 2.54 (s, 1H), 2.31 (t, $J=12\text{Hz}$, 1H), 1.96-2.03 (m, 5H), 1.68-1.79 (m, 5H), 1.68-1.79 (m, 2H)

IR (DCM): 1660.7 cm^{-1}

Biological Activity**Radioligand Binding Assays:**

The affinity of test compounds for M₂ and M₃ muscarinic receptor subtypes was determined by [³H]-N-methylscopolamine binding studies using rat heart and

5 submandibular gland respectively as described by Moriya et al., (*Life Sci.*, 1999,64(25):2351-2358) with minor modifications.

Membrane preparation: Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of

10 homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min. The pellet thus obtained was resuspended in same volume of assay buffer (HEPES 20 mM, EDTA 5mM, pH 7.4) and were stored at -70°C until the time of assay.

15 **Ligand binding assay:** The compounds were dissolved and diluted in DMSO. The membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay buffer (HEPES 20 mM, pH 7.4) at 24-25°C for 3h. Non-specific binding was determined in the presence of 1 µM atropine . The incubation was terminated by vacuum filtration over GF/B fiber filters(Wallac). The filters were then washed with ice

20 cold 50mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was counted. The IC₅₀ & Kd were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant Ki was calculated from competitive binding studies by using Cheng & Prusoff equation (*Biochem Pharmacol*, 1973,22: 3099-3108), Ki = IC₅₀

25 / (1+L/Kd), where L is the concentration of [³H]NMS used in the particular experiment.

Functional Experiments using isolated rat bladder:**Methodology:**

Animals were euthanized by overdose of urethane and whole bladder was isolated

and removed rapidly and placed in ice cold Tyrode buffer with the following composition (mMol/L) NaCl 137; KCl 2.7; CaCl₂ 1.8; MgCl₂ 0.1; NaHCO₃ 11.9; NaH₂PO₄ 0.4; Glucose 5.55 and continuously gassed with 95% O₂ and 5 % CO₂.

The bladder was cut into longitudinal strips (3mm wide and 5-6 mm long) and mounted in 10 ml organ baths at 30° C, with one end connected to the base of the tissue holder and the other end connected to a polygraph through a force displacement transducer. Each tissue was maintained at a constant basal tension of 2 g and allowed to equilibrate for 1 hour during which the PSS was changed every 15 min. At the end of equilibration period, the stabilization of the tissue contractile response was assessed with 1µMol/L of Carbachol consecutively for 2-3 times.

Subsequently, a cumulative concentration response curve to carbachol (10^{-9} mol/L to 3×10^{-5} mol/L) was obtained. After several washes, once the baseline was achieved, cumulative concentration response curve was obtained in the presence of NCE (NCE added 20 min. prior to the second CRC).

The contractile results were expressed as % of control E max. ED50 values were calculated by fitting a non-linear regression curve (Graph Pad Prism). pKB values were calculated by the formula $pKB = -\log [(\text{molar concentration of antagonist}/(\text{dose ratio}-1))]$

where,

dose ratio = ED50 in the presence of antagonist/ED50 in the absence of antagonist.

The results are listed in Tables II, III and IV.

In -Vitro testsTable II

	Receptor Binding Assay Ki (nM)			Functional Assay K _B (nM)
	M ₂	M ₃	Selectivity	
Compound No.22	2263	94	24.07	27.5
Compound No.41	2944	47	62.64	32.35
Compound No.65	1370	33	41.52	4.0
Compound No.66	237	18.4	12.88	5.0
Compound No. 81	564	12.4	45.48	7.95
Compound No. 82	645.7	11.74	5	9.12
Tolterodine	6.91	7.07	0.98	2.0
Oxybutynin	6.97	0.95	7.34	2.0
Atropine	0.5	0.6	0.83	

Table III

Compound No.	M ₃		M ₂		Rat Bladder
	Ki (nm)	PKi	Ki (nm)	pKi	pK _B
22	94	7.03	2263	5.65	7.57
23	530	6.28	> 1000	< 6	5.64
24	490	6.31	> 1000	< 6	5.42
25	1700	5.77	> 1000	< 6	6.54
28	150	6.82	> 1000	< 6	ND
29	97	7.01	> 1000	< 6	ND
30	833	6.08	> 0000	<5	ND
31	233	6.63	1592	5.8	ND
35	429	6.37	1179	< 6	7.61
38	1560	5.81	> 1000	< 6	6.54
41	47	7.33	2944	5.53	7.69
42	55	7.25	2197	5.66	7.12
49	1000	6.00	> 1000	< 6	6.2
50	1200	5.92	> 1000	< 6	6.86
52	370	6.43	> 1000	< 6	5.51
55	380	6.42	> 1000	< 6	ND
57	240	6.62	> 1000	< 6	5.73
64	68	7.2	2995	5.6	7.56
65	33	7.53	1370	5.87	8.4
66	18.43	7.81	181.8	6.94	8.49
67	39	7.41	1424	5.85	7.42
68	108	6.97	> 1000	< 6	ND
69	1416	5.85	>10000	< 5	ND
70	750	6.12	>10000	< 5	ND
72	21	7.68	1531	5.82	7.18
81	12.4	7.94	564	6.28	7.95
82	11.74	7.93	645.7	6.19	9.12
Tolterodine	7.07	8.15	6.91	8.16	2.0
Atropine	0.6	9.6	0.5	9	-

Table IV

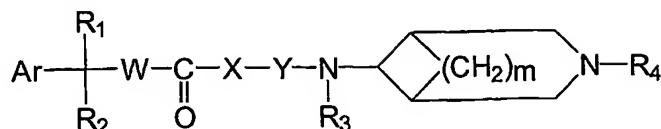
Compound No.	Receptor Binding Assay (pKi)	
	M ₂	M ₃
85	<6	<6
86	<6	<6
87	<6	<6
88	<6	<6
89	<6	<6
90	<6	6.44
91	4	5.56
92	<5	<5
93	<6	<6
94	<6	<6
95	<6	<6
96	<6	<6
97	<6	<6
98	<6	<6
Tolterodine	8.30	8.18

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WE CLAIM:

1. A compound having the structure of Formula I :

5



10

Formula I

15

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantioners, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

20

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from straight or branched lower alkyl (C₁-C₄), trifluoromethyl, methylenedioxy, cyano, hydroxy, halogen (e.g. F, Cl, Br, I), nitro, lower alkoxy (C₁-C₄), aryloxy, amino or lower alkylamino;

25

R₁ represents C₃-C₉ cycloalkyl ring, a C₃-C₉ cyclo alkenyl ring, an aryl or a heteroaryl ring having 1 to 2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or a heteroaryl ring may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), unsubstituted amino or lower alkyl (C₁-C₄) amino;

30

R₂ represents a hydrogen, hydroxy, amino, alkoxy, alkenyloxy, alkynyloxy, carbamoyl or halogen (e.g. F, Cl, Br, I);

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR, or no atom, where R is H or lower alkyl (C₁-C₄);

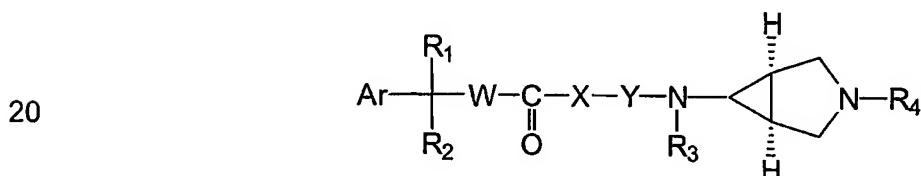
Y represents $(CHR_5)_q CO$ wherein R_5 represents hydrogen or methyl; or
y represents $(CH_2)_q$ wherein q represents 0 to 4;

m represents 0 to 2;

R_3 represents hydrogen, lower alkyl or $CO_2C(CH_3)_3$;

5 R_4 represents hydrogen, C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3
10 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, carboxylic acid, nitro, lower alkoxy carbonyl, halogen, lower alkoxy, amino, lower alkylamino, loweralkyl carbonyl amino, loweralkyl thiocarbonyl amino or loweralkyl carbonyl amino sulphonyl and
15 pharmaceutically acceptable salts thereof.

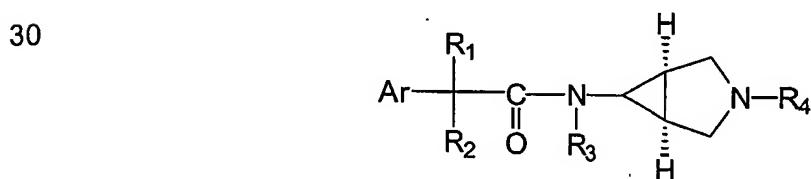
2. The compound according to claim 1 having the structure of Formula II



Formula II

25 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₂, R₃, R₄, W, X and Y are as defined for Formula I.

3. The compound according to claim 1 having the structure of Formula III

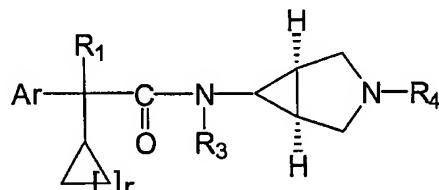


Formula III

5 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantioners, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein Ar, R₁, R₂, R₃, and R₄ are as defined for Formula I.

4. The compound according to claim 1 having the structure of Formula IV

10



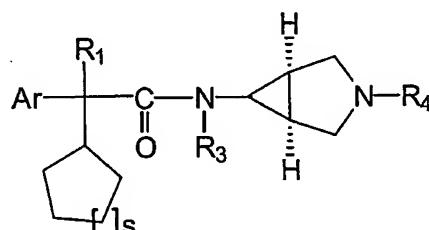
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Formula IV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₃, and R₄, are as defined for Formula I and r is 1 to 4.

5. A Compound according to claim 1 having the structure of Formula V

25



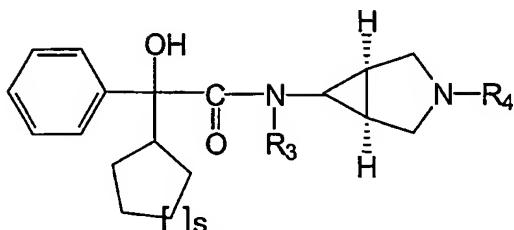
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Formula V

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₃ and R₄ are as defined for Formula I and s is 1 to 3.

6. The compound according to claim 5 having the structure of Formula VI

5



10

Formula VI

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites wherein R₃, R₄ and s are as defined for Formula V.

7. A compound selected from the group consisting of :

- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-diphenyl acetamide (Compound No.1),
- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di (4-fluoro phenyl) acetamide (Compound No.2),
- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenyoxy)-2,2-diphenyl acetamide (Compound No.3),
- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propenyoxy)-2,2-di(4-fluorophenyl) acetamide (Compound No.4),
- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-propyloxy-2,2-diphenyl acetamide (Compound No.5),
- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-propyloxy-2,2-di(4-fluoro phenyl) acetamide (Compound No.6),
- (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-(2-propynyoxy)-2,2-diphenyl acetamide (Compound No.7),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(2-furyl) acetamide (Compound No.8),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-hydroxy-2,2-di(2-thienyl) acetamide (Compound No.9),

5 ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxy carbonyl)butyl-1-(2-hydroxy-2,2-diphenyl)acetate (Compound No.10),

 ($1\alpha,5\alpha,6\alpha$)-3-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butylcarbonyl)propyl-1-(2-hydroxy-2,2-diphenyl)acetate (Compound No.11),

10 ($1\alpha,5\alpha,6\alpha$)-3-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxy carbonyl propyl-1-(2-propyloxy-2,2-diphenyl) acetate (Compound No.12),

 ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxy carbonyl)butyl-1-(2-propyloxy-2,2-diphenyl)acetate(Compound No.13),

15 ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxy carbonyl) butyl-1-(2-(2-propenyl)oxy)-2,2-diphenyl) acetate (Compound No.14),

 ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxy carbonyl)butyl-1-(2-hydroxy-2,2-di(4-fluorophenyl))acetate (Compound No.15),

20 ($1\alpha,5\alpha,6\alpha$)-4-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-tert-butyloxy carbonyl butyl-1-(2-propyloxy-2,2-di(4-fluorophenyl)) acetate(Compound No.16),

 ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido-2- (2-propyloxy)-2,2-diphenyl acetate (Compound No.17),

25 ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido- 2- (2-propenyl)oxy)-2,2-diphenyl acetate(Compound No.18),

($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-propionamido- 2- (2-propenyoxy)-2,2-diphenyl acetate (Compound No.19),

($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-propionamido- 2- 2-propyloxy)-2,2-diphenyl acetate (Compound No.20),

5 ($1\alpha,5\alpha,6\alpha$)-1-(6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl))-N-acetamido -2-hydroxy-2,2-di(4-fluorophenyl) acetate(Compound No.21),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy- 2-phenyl acetamide (Compound No.22),

10 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,5-difluorobenzyl))- 2- cyclo hexyl-2-hydroxy-2-phenyl acetamide (Compound No.23),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-bromobenzyl))-2-cyclo hexyl-2-hydroxy-2-phenyl acetamide (Compound No.24),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2,6-difluorobenzyl)) -2- cyclo hexyl- 2-hydroxy-2-phenyl acetamide (Compound No.25),

15 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylbenzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.26),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.27),

20 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(2,3-dihydrobenzofuran-5-yl)ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.28),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(3,4-methylenedioxyphenyl)ethyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.29),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-(2,3-dihydrobenzofuran-5-yl)acetyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.30),

25 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(benzofuran-5-yl)ethyl))-2-cyclo hexyl-2-hydroxy-2-phenyl acetamide (Compound No.31),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-methyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.32),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-ethyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.33),

5 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-propyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.34),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propargyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.35),

10 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.36),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-propyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.37),

15 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-cyclopropyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.38),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-butyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.39),

20 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3-methyl-2-butenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.40),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.41),

25 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(3,4-methylenedioxybenzyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.42),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(6,6-dimethyl-2,4-heptadiynyl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.43),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzoyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.44),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-formyl-fur-5-yl))-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.45),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(aniline)thiourea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.46),

5 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(methyl, 4-amino-1-phenyl acetate)urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.47),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-amino-1-phenyl acetic acid)urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.48),

10 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methylphenyl-1-sulphonamide)urea)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.49),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl) acetamide (Compound No.50),

15 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide (Compound No.51),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-phenoxyphenyl) acetamide (Compound No.52),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide (Compound No.53).

20 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(3,4-methylenedioxyphenyl) acetamide(Compound No.54),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-hydroxy-2-(4-tertbutylphenyl) acetamide (Compound No.55).

25 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl) acetamide (Compound No.56),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl) acetamide (Compound No.57),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide (Compound No.58),

5 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.59),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-ethyl)-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.60),

10 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclohexyl-2-(2-propenyloxy)-2-phenyl acetamide (Compound No.61),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.62),

15 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2,4-difluorobenzyl))-2-cyclohexyl-2-methoxy-2-phenyl acetamide (Compound No.63),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.64),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.65),

20 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(3,4-methylenedioxyphenyl)ethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.66),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-phenylethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.67),

($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(2,3-dihydrobenzofuran-5-yl)ethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.68),

25 ($1\alpha,5\alpha,6\alpha$)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-methyl-pyrid-6-yl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.69),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(1-(2,3-dihydrobenzofuran-5-yl)acetyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.70),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(2-(benzofuran-5-yl)ethyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.71),

5 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-2-cycloheptyl-2-hydroxy-2-phenyl acetamide (Compound No.72),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cycloheptyl-2-hydroxy-2-phenyl acetamide (Compound No.73),

10 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.74),

2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) acetamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide. (Compound No.75),

15 3-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.76),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl)-3-cyclohexyl-3-hydroxy-3-phenyl propionamide (Compound No.77),

20 2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) acetamido)-3-cyclohexyl-3-hydroxy-3-phenyl propionamide (Compound No.78),

2-Amino-((1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-benzyl) propionamido)-2-cyclohexyl-3-hydroxy-3-phenyl propionamide (Compound No.79),

(1 α ,5 α ,6 α)-2-[6-N-(3-benzyl-3-azabicyclo[3.1.0]hexyl)-N-propionamido-2-cyclohexyl-2-hydroxy-2-phenyl acetate (Compound No.80),

(2R)(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.81),

(2R)(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-3-(3,4-methylenedioxyphenyl)ethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide
(Compound No.82),

5 (2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide succinate salt. (Compound No.83),

(2R)-(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-3-(4-methyl-3-pentenyl))-2-cyclopentyl-2-hydroxy-2-phenyl acetamide L-(+)-tartrate salt.
(Compound No.84),

10 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No.85),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-fluorophenyl) acetamide (Compound No.86),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl)acetamide (Compound No.87),

15 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-hydroxy-2-(4-methylphenyl)acetamide (Compound No.88),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.89),

20 (1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cycloheptyl-2-hydroxy-2-phenyl acetamide (Compound No.90),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclobutyl-2-hydroxy-2-phenyl acetamide (Compound No.91),

(1 α ,5 α ,6 α)-6-N-(3-azabicyclo[3.1.0]hexyl)-2-cyclopropyl-2-hydroxy-2-phenyl acetamide (Compound No.92),

($1\alpha,5\alpha,6\alpha$)-1-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-acetamido-2-hydroxy-2-cyclohexyl-2-phenylacetate (Compound No.93),

($1\alpha,5\alpha,6\alpha$)-1-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-propionamido-2-hydroxy-2-cyclohexyl-2-phenylacetate (Compound No.94),

5 ($1\alpha,5\alpha,6\alpha$)-4-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-(tert-butyloxycarbonyl)butyl-1-[2-hydroxy-2,2-bis(4-fluorophenyl)]acetate (Compound No.95),

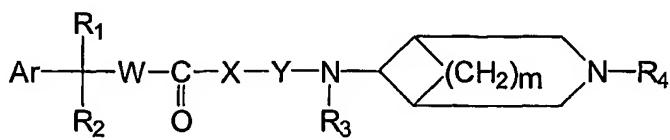
($1\alpha,5\alpha,6\alpha$)-4-[6N-(3-azabicyclo[3.1.0]hexyl)]-N-(tert-butyloxycarbonyl)butyl-1-[2-propyloxy-2,2-bis(4-fluorophenyl)]acetate (Compound No.96),

10 ($1\alpha,5\alpha,6\alpha$)-6N-(3-azabicyclo[3.1.0]hexyl)-2,2-diphenyl acetamide (Compound No.97),

($1\alpha,5\alpha,6\alpha$)-6N-(3-azabicyclo[3.1.0]hexyl)-2-cyclohexyl-2-methoxy-2-phenylacetamide (Compound No.98).

- 8. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any of claims 1-7 together with pharmaceutically acceptable carriers, excipients or diluents.
- 15
- 9. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I
- 20

25



Formula I

30 and its pharmaceutically acceptable salts, pharmaceutically acceptable

solvates, esters, enantioners, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from straight or branched lower alkyl (C₁-C₄), trifluoromethyl, methylenedioxy, cyano, hydroxy, halogen (e.g. F, Cl, Br, I), nitro, lower alkoxy (C₁-C₄), aryloxy, amino or lower alkylamino;

R₁ represents C₃-C₉ cycloalkyl ring, a C₃-C₉ cyclo alkenyl ring, an aryl or a heteroaryl ring having 1 to 2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms; the aryl or a heteroaryl ring may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), unsubstituted amino or lower alkyl (C₁-C₄) amino;

R₂ represents a hydrogen, hydroxy, amino, alkoxy, alkenyloxy, alkynyloxy, carbamoyl or halogen (e.g. F, Cl, Br, I);

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR, or no atom, where R is H or lower alkyl (C₁-C₄);

Y represents (CHR₅)_q CO wherein R₅ represents hydrogen or methyl; or Y represents (CH₂)_q wherein q represents 0 to 4;

m represents 0 to 2;

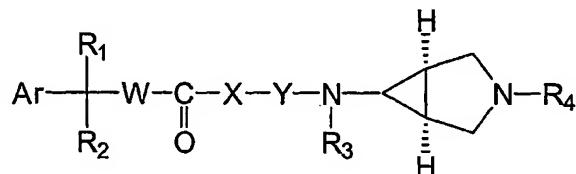
R₃ represents hydrogen, lower alkyl or CO₂C(CH₃)₃;

R₄ represents hydrogen, C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from

the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, carboxylic acid, nitro, lower alkoxy carbonyl, halogen, lower alkoxy, amino, lower alkylamino, loweralkyl carbonyl amino, loweralkyl thiocarbonyl amino or loweralkyl carbonyl amino sulphonyl.

5 10. The method according to claim 9 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, where the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of
10 Formula II

15



Formula II

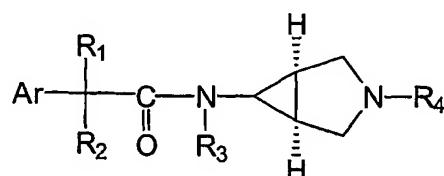
20

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₂, R₃, R₄, W, X and Y are as defined for Formula I.

25 11.

The method according to claim 9 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of
30 Formula III

35

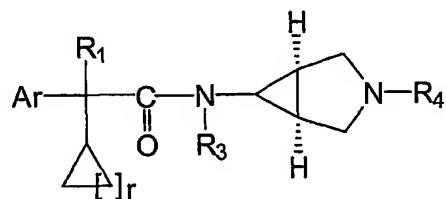


Formula III

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₂, R₃, and R₄ are as defined for Formula I.

5 12. The method according to claim 9 for treatment or prophylaxis of an animal or a
human suffering from a disease or disorder of the respiratory, urinary and
gastrointestinal systems wherein the disease or disorder is mediated through
muscarinic receptors, comprising administering to said animal or human, a
therapeutically effective amount of a compound having the structure of

10 Formula IV

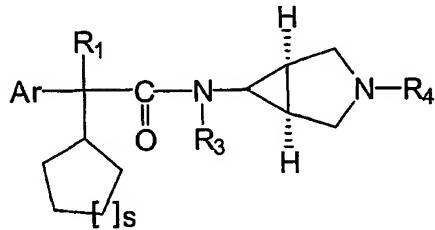


15

Formula IV

20 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₃, and R₄, are as defined for
Formula I and r is 1 to 4.

25 13. The method according to claim 9 for treatment or prophylaxis of an animal or a
human suffering from a disease or disorder of the respiratory, urinary and
gastrointestinal systems, wherein the disease or disorder is mediated through
muscarinic receptors, comprising administering to said animal or human, a
therapeutically effective amount of a compound having the structure of
Formula V



30

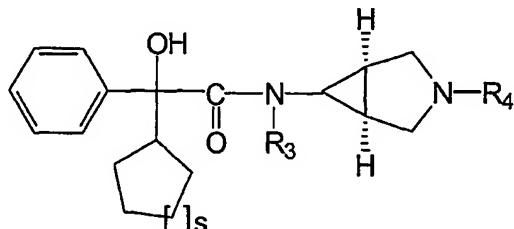
35 Formula V

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₃ and R₄ are the same as defined for Formula I and s is 1 to 3.

5 14. The method according to claim 9 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of compound having the structure of

10 10 Formula VI

15



20

Formula VI

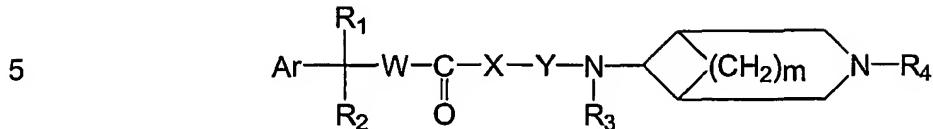
and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxide, polymorphs, prodrugs, metabolites wherein R₃, R₄ and s are the same as defined for Formula V..

25 15. The method according to claim 9 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesia.

30 16. The method according to claim 10 wherein the disease or disorders is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructure pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesia.

17. The method according to claim 11 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.
- 5 18. The method according to claim 12 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.
- 10 19. The method according to claim 13 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.
- 15 20. The method according to claim 14 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.
- 20 21. The method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of the pharmaceutical composition according to claim 8.
- 25 22. The method according to claim 21 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

23. A process of preparing a compound of Formula I,



10 Formula I

10 and its pharmaceutical acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites wherein

15 Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from straight or branched lower alkyl (C₁-C₄), trifluoromethyl, methylenedioxy, cyano, hydroxy, halogen (e.g. F, Cl, Br, I), nitro, lower alkoxy (C₁-C₄), aryloxy, amino or lower alkylamino;

20 R₁ represents C₃-C₉ cycloalkyl ring, a C₃-C₉ cyclo alkenyl ring, an aryl or a heteroaryl ring having 1 to 2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms; the aryl or a heteroaryl ring may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower 25 alkoxycarbonyl, halogen, lower alkoxy (C₁-C₄), unsubstituted amino or lower alkyl (C₁-C₄) amino;

R₂ represents a hydrogen, hydroxy, amino, alkoxy , alkenyloxy, alkynyoxy, carbamoyl or halogen (e.g. F, Cl, Br, I);

W represents (CH₂)_p, where p represents 0 to 1;

30 X represents an oxygen, sulphur, NR, or no atom, where R is H or lower alkyl (C₁-C₄);

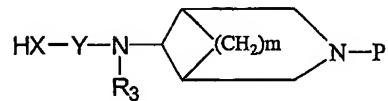
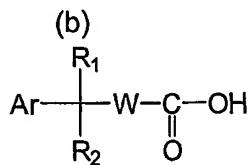
Y represents (CHR₅)_q CO wherein R₅ represents hydrogen or methyl; or
Y represents (CH₂)_q wherein q represents 0 to 4;

m represents 0 to 2;

R₃ represents hydrogen, lower alkyl or CO₂C(CH₃)₃;

R₄ represents hydrogen.

5 (a) condensing a compound of Formula VII with a compound of Formula VIII

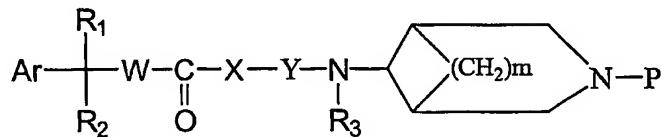


10

Formula VII**Formula VIII**

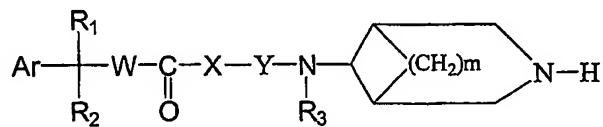
wherein Ar, R₁, R₂, R₃, W, X, Y and m have the same meanings as defined earlier, P is any group which can be used to protect an amino group, in the presence of a condensing agent to give a protected compound of Formula IX, and

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**Formula IX**

(b) deprotecting the compound of Formula IX in the presence of a deprotecting agent to give a compound of Formula X,

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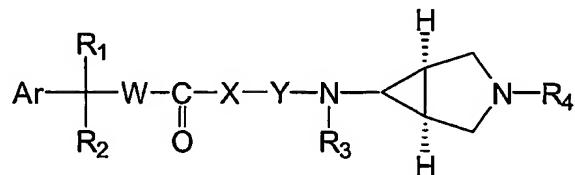
**Formula X**

wherein Ar, R₁, R₂, R₃, W, X, Y, m and P are the same as defined earlier.

24. The process according claim 23 wherein the group P is selected from the group consisting of benzyl and tert-butyloxycarbonyl.

25. The process according to claim 23 wherein the condensing agent is selected from the group consisting of 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

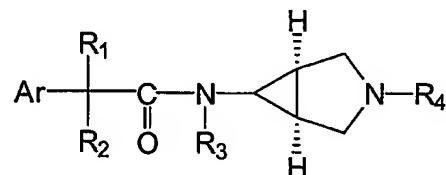
5 26. The process according to claim 23 for preparing a compound of Formula II wherein R₄ is hydrogen.



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Formula II

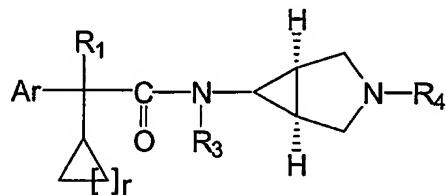
27. The process according to claim 23 wherein the compound of Formula III is prepared wherein R₄ is hydrogen.



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Formula III

28. The process according to Claim 23 wherein the compound of Formula IV is prepared wherein R₄ is hydrogen.

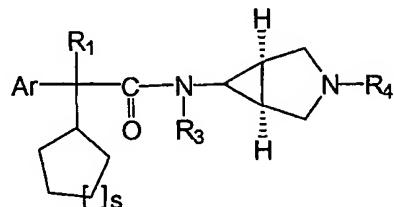


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Formula IV

29. The process according to Claim 28 wherein the compound of Formula V is prepared wherein R₄ is hydrogen.

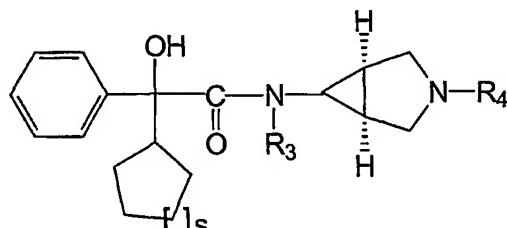
5

**Formula V**

30. The process according to Claim 29 wherein the compound of Formula VI is prepared wherein R₄ is hydrogen.

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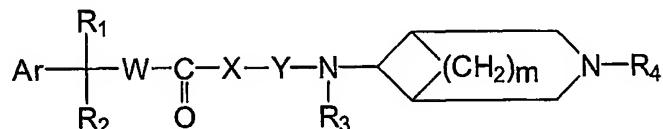
15

**Formula VI**

31. A process of preparing a compound of Formula I,

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**Formula I**

and its pharmaceutical acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from straight or branched lower alkyl (C₁-

C₄), trifluoromethyl, methylenedioxy, cyano, hydroxy, halogen (e.g. F, Cl, Br, I), nitro, lower alkoxy (C₁-C₄), aryloxy, amino or lower alkylamino;

5 R₁ represents C₃-C₉ cycloalkyl ring, a C₃-C₉ cyclo alkenyl ring, an aryl or a heteroaryl ring having 1 to 2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms; the aryl or a heteroaryl ring may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), trifluoromethyl, cyano, hydroxy, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C₁-C₄), unsubstituted amino or lower alkyl (C₁-C₄) amino;

10 R₂ represents a hydrogen, hydroxy, amino, alkoxy , alkenyloxy, alkynyloxy, carbamoyl or halogen (e.g. F, Cl, Br, I);

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR, or no atom, where R is H or lower alkyl (C₁-C₄);

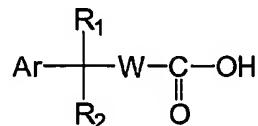
15 Y represents (CHR₅)_q CO wherein R₅ represents hydrogen, or methyl; or Y represents (CH₂)_q wherein q represents 0 to 4;

m represents 0 to 2;

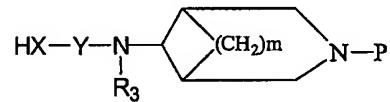
R₃ represents hydrogen, lower alkyl or CO₂C(CH₃)₃;

20 R₄ represents C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, carboxylic acid, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino, lower alkylamino, loweralkyl carbonyl amino, loweralkyl thiocarbonyl amino or loweralkyl carbonyl amino sulphonyl, comprising

(a) condensing a compound of Formula VII with a compound of Formula VIII

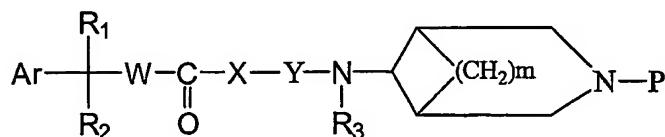


Formula VII



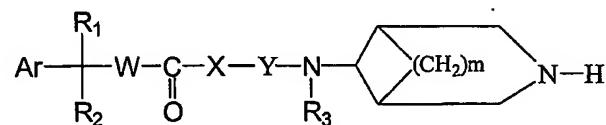
Formula VIII

5 wherein Ar, R₁, R₂, R₃, W, X, Y and m have the same meanings as defined earlier, P is any group which can be used to protect an amino group, in the presence of a condensing agent to give a protected compound of Formula IX,



10 Formula IX

(b) deprotecting the compound of Formula IX in the presence of a deprotecting agent to give a compound of Formula X,



Formula X

wherein Ar, R₁, R₂, R₃, W, X, Y, m and P are the same as defined earlier, and

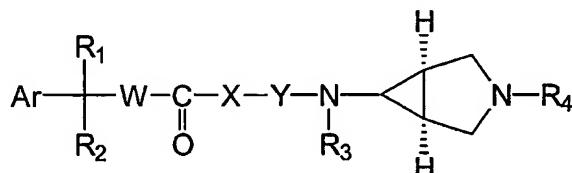
20 (c) N-alkylating or benzylating the compound of Formula X with a suitable alkylating or benzylating agent L-R₄ wherein L is a leaving group and R₄ is as defined earlier, to give a compound of Formula I.

32. The process according claim 31 wherein the group P is selected from the group consisting of benzyl and tert-butyloxycarbonyl.

33. The process according to claim 31 wherein the condensing agent is selected from the group consisting of 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

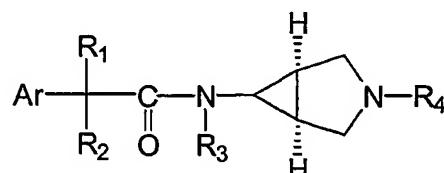
34. The process according to claim 31 for preparing a compound of Formula II.

5

**Formula II**

35. The process according to claim 31 wherein the compound of Formula III is prepared.

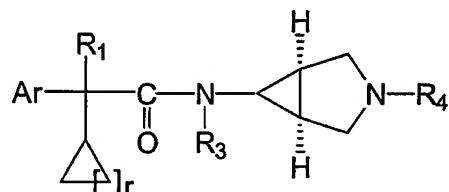
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**Formula III**

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36. The process according to Claim 31 wherein the compound of Formula IV is prepared.

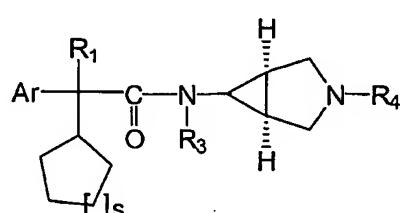
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**Formula IV**

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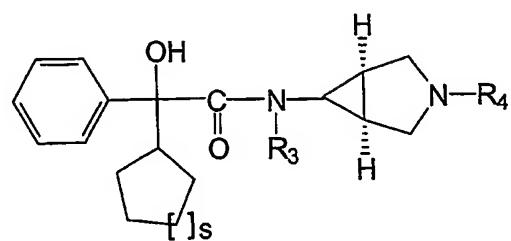
37. The process according to Claim 36 wherein the compound of Formula V is prepared.

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**Formula V**

38. The process according to Claim 37 wherein the compound of Formula VI is prepared.

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Formula VI

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB UZ/05220

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D209/52	A61K31/403	A61P31/02	C07D405/14	C07D409/14
	C07D405/06	C07D405/12	A61P11/00		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 930 298 A (BANYU PHARMA CO LTD) 21 July 1999 (1999-07-21) cited in the application claims	1-38
A	WO 97 45414 A (BANYU PHARMA CO LTD ;KAWAKAMI KUMIKO (JP); NOMOTO TAKASHI (JP); OH) 4 December 1997 (1997-12-04) cited in the application abstract; claims	1-38
A	EP 0 823 423 A (BANYU PHARMA CO LTD) 11 February 1998 (1998-02-11) cited in the application claims	1-38
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the International search report
4 March 2003	17/03/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International	Application No
PCT/1 J2/05220	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 863 141 A (BANYU PHARMA CO LTD) 9 September 1998 (1998-09-09) cited in the application claims ---	1-38
A	US 5 703 091 A (MUNSCHAUER RAINER ET AL) 30 December 1997 (1997-12-30) column 1 -column 2 column 3, line 14 ---	1-38
A	US 5 914 338 A (JEPPESEN LONE ET AL) 22 June 1999 (1999-06-22) claims ---	1-38
A	US 5 397 800 A (ALKER DAVID ET AL) 14 March 1995 (1995-03-14) column 1 -column 2 -----	1-38

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/IB 02/05220

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9–22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1–38 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-38 (in part)

The present claims relate in part to "prodrugs or metabolites" of structurally defined compounds. Since the description is silent about possible meanings of these definitions in terms of structural features ("metabolites" could e. g. mean fragments obtained by the cleavage of the amide bond, i. e. compounds known already from D1-D4) unclarity (Art. 6 PCT) arises to such an extent that a meaningful search in this respect is impossible. The search has been limited to compounds structurally defined in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Info on patent family members

International application No
PCT/IB 02/05220

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0930298	A	21-07-1999	AT 229941 T		15-01-2003
			AU 716050 B2		17-02-2000
			AU 3635197 A		25-02-1998
			BG 103114 A		30-11-1999
			BR 9711108 A		17-08-1999
			DE 69718026 D1		30-01-2003
			EE 9900038 A		16-08-1999
			EP 0930298 A1		21-07-1999
			JP 3063164 B2		12-07-2000
			NO 990472 A		01-02-1999
			NZ 333842 A		25-05-2001
			SK 12299 A3		16-05-2000
			CN 1226888 A		25-08-1999
			CZ 9900331 A3		14-07-1999
			HR 970426 A1		31-08-1998
			HU 9902381 A2		29-11-1999
			WO 9805641 A1		12-02-1998
			JP 3282617 B2		20-05-2002
			JP 2000178231 A		27-06-2000
			JP 3282618 B2		20-05-2002
			JP 2000169449 A		20-06-2000
			KR 2000022214 A		25-04-2000
			PL 331431 A1		19-07-1999
			TR 9900204 T2		21-01-2000
			TR 200001482 T2		21-11-2000
			US 6040449 A		21-03-2000
			US 5948792 A		07-09-1999
			ZA 9706813 A		11-02-1998
WO 9745414	A	04-12-1997	AU 2793197 A		05-01-1998
			WO 9745414 A1		04-12-1997
EP 0823423	A	11-02-1998	AU 700837 B2		14-01-1999
			AU 5513996 A		18-11-1996
			EP 0823423 A1		11-02-1998
			JP 2993124 B2		20-12-1999
			US 5750540 A		12-05-1998
			CA 2218479 A1		31-10-1996
			WO 9633973 A1		31-10-1996
EP 0863141	A	09-09-1998	AT 205490 T		15-09-2001
			AU 7145996 A		30-04-1997
			DE 69615214 D1		18-10-2001
			DE 69615214 T2		27-06-2002
			EP 0863141 A1		09-09-1998
			US 6130232 A		10-10-2000
			CA 2234619 A1		17-04-1997
			WO 9713766 A1		17-04-1997
US 5703091	A	30-12-1997	DE 4341403 A1		08-06-1995
			AT 194620 T		15-07-2000
			AU 680583 B2		31-07-1997
			AU 1240395 A		19-06-1995
			BR 9408246 A		27-05-1997
			CA 2177602 A1		08-06-1995
			DE 69425273 D1		17-08-2000
			DE 69425273 T2		18-01-2001
			WO 9515327 A1		08-06-1995

INTERNATIONAL SEARCH REPORT

Info on patent family members

International application No
PCT/EP 92/05220

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
US 5703091	A	EP ES FI IL JP NO	0731802 A1 2148476 T3 962324 A 111861 A 9506346 T 962286 A	18-09-1996 16-10-2000 03-06-1996 17-08-1999 24-06-1997 03-06-1996	
US 5914338	A	22-06-1999	AU CA WO EP JP JP ZA	2287197 A 2250843 A1 9736906 A1 0891363 A1 3162727 B2 11509864 T 9702790 A	22-10-1997 09-10-1997 09-10-1997 20-01-1999 08-05-2001 31-08-1999 02-10-1997
US 5397800	A	14-03-1995	FI JP JP CA WO EP IE PT	922143 A 7119213 B 5501887 T 2068527 A1 9205172 A2 0510129 A1 913210 A1 98929 A ,B	12-05-1992 20-12-1995 08-04-1993 14-03-1992 02-04-1992 28-10-1992 25-02-1992 31-07-1992